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Enzyme replacement therapy for Anderson-Fabry disease (Review)

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[Intervention Review]

Enzyme replacement therapy for Anderson-Fabry disease

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ABSTRACT

Background

Anderson-Fabry disease is an X-linked defect of glycosphingolipid metabolism. Progressive renal insufficiency is a major source of morbidity, additional complications result from cardio- and cerebro-vascular involvement. Survival is reduced among affected males and symptomatic female carriers.

This is an update of a Cochrane review first published in 2010, and previously updated in 2013.

Objectives

To evaluate the effectiveness and safety of enzyme replacement therapy compared to other interventions, placebo or no interventions, for treating Anderson-Fabry disease.

Search methods

We searched the Cystic Fibrosis and Genetic Disorders Group's Inborn Errors of Metabolism Trials Register (date of the most recent search: 08 July 2016). We also searched 'Clinical Trials' on *The Cochrane Library*, MEDLINE, Embase and LILACS (date of the most recent search: 24 September 2015).

Selection criteria

Randomized controlled trials of agalsidase alfa or beta in participants diagnosed with Anderson-Fabry disease.

Data collection and analysis

Two authors selected relevant trials, assessed methodological quality and extracted data.

Main results

Nine trials comparing either agalsidase alfa or beta in 351 participants fulfilled the selection criteria.

Both trials comparing agalsidase alfa to placebo reported on globotriaosylceramide concentration in plasma and tissue; aggregate results were non-significant. One trial reported pain scores measured by the Brief Pain Inventory severity, there was a statistically significant improvement for participants receiving treatment at up to three months, mean difference -2.10 (95% confidence interval -3.79 to -0.41;

at up to five months, mean difference -1.90 (95% confidence interval -3.65 to -0.15); and at up to six months, mean difference -2.00 (95% confidence interval -3.66 to -0.34). There was a significant difference in the Brief Pain Inventory pain-related quality of life at over five months and up to six months, mean difference -2.10 (95% confidence interval -3.92 to -0.28) but not at other time points. Death was not an outcome in either of the trials.

One of the three trials comparing agalsidase beta to placebo reported on globotriaosylceramide concentration in plasma and tissue and showed significant improvement: kidney, mean difference -1.70 (95% confidence interval -2.09 to -1.31); heart, mean difference -0.90 (95% confidence interval -1.18 to -0.62); and composite results (renal, cardiac, and cerebrovascular complications and death), mean difference -4.80 (95% confidence interval -5.45 to -4.15). There was no significant difference between groups for death; no trials reported on pain.

Only two trials compared agalsidase alfa to agalsidase beta. One of them showed no significant difference between the groups regarding adverse events, risk ratio 0.36 (95% confidence interval 0.08 to 1.59), or any serious adverse events; risk ratio 0.30; (95% confidence interval 0.03 to 2.57).

Two trials compared different dosing schedules of agalsidase alfa. One of them involved three different doses (0.2 mg/kg every two weeks; 0.1 mg/kg weekly and; 0.2 mg/kg weekly), the other trial evaluated two further doses to the dosage schedules: 0.4 mg/kg every week and every other week. Both trials failed to show significant differences with various dosing schedules on globotriaosylceramide levels. No significant differences were found among the schedules for the primary efficacy outcome of self-assessed health state, or for pain scores.

One trial comparing agalsidase alfa to agalsidase beta showed no significant difference for any adverse events such as dyspnoea and hypertension.

The methodological quality of the included trials was generally unclear for the random sequence generation and allocation concealment.

Authors' conclusions

Trials comparing enzyme replacement therapy to placebo show significant improvement with enzyme replacement therapy in regard to microvascular endothelial deposits of globotriaosylceramide and in pain-related quality of life. There is, however, no evidence identifying if the alfa or beta form is superior or the optimal dose or frequency of enzyme replacement therapy. With regards to safety, adverse events (i.e., rigors, fever) were more significant in the agalsidase beta as compared to placebo. The long-term influence of enzyme replacement therapy on risk of morbidity and mortality related to Anderson-Fabry disease remains to be established. This review highlights the need for continued research into the use of enzyme replacement therapy for Anderson-Fabry disease.

PLAIN LANGUAGE SUMMARY

Treatment for Anderson-Fabry disease

Background

Anderson-Fabry disease, a rare disorder, is caused by a deficiency of the enzyme alpha-galactosidase A. This leads to the build-up of a fatty material called globotriaosylceramide in various cells in the body. Globotriaosylceramide is formed of three sugars and a fatty substance called ceramide, and is found in most cells of the body. Untreated individuals may suffer from pain, skin, eye and gastrointestinal problems. Fabry disease may cause potentially life-threatening complications such as kidney damage, heart attack and stroke. One type of treatment available is enzyme replacement therapy with either agalsidase alfa or beta, which replaces the missing or deficient enzyme.

Search date

The evidence is current to: 08 July 2016.

Study characteristics

Nine studies enrolled 351 participants. The studies used different formulations of the enzyme, Agalsidase alfa or beta, and compared them to placebo (a 'dummy' treatment) or to each other. Comparison was also made in regard to different dosing schedules.

Key results

Two studies comparing agalsidase alfa to placebo reported on globotriaosylceramide concentration in plasma. The combined effects were not significant between the treatment and placebo groups. The study that reported pain and pain-related quality of life showed an improvement for participants receiving treatment over the six-month observation period. Death was not an outcome in either study.

One of the three studies comparing agalsidase beta to placebo reported on globotriaosylceramide and showed improvement in kidney, heart and composite results. There was no significant difference for death and no studies reported on pain.

Only two studies compared agalsidase alfa to agalsidase beta. One of them showed no significant difference for any adverse events such as dyspnoea, hypertension and gastrointestinal symptoms - these are not adverse events as gastrointestinal problems are actually a symptom, as may be hypertension in the context of renal disease.

Two studies compared different dosing schedules of agalsidase alfa. No differences were found among the schedules for self-assessed health state or for pain scores.

In summary, studies comparing enzyme replacement therapy to placebo show significant results in regard to microvascular endothelial deposits of globotriaosylceramide and in pain-related quality of life. There is, however, no evidence identifying if the alfa or beta form is superior, though included trials were small in sample size. With regards to safety, adverse events (i.e., rigors, fever) were more significant with agalsidase beta as compared to placebo.

Quality of the evidence
From the information available in most of the study reports, we were not able to clearly judge whether all volunteers had equal chances of being in either of the treatment groups and whether they would have known in advance or during the study which treatment they were receiving.

SUMMARY OF FINDINGS

Summary of findings for the main comparison.

Enzyme replacement therapy for Anderson-Fabry disease

Patient or population: Anderson-Fabry disease

Settings: outpatients

Intervention: agalsidase alfa

Comparison: placebo

Outcomes	Illustrative comparative risks (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Placebo	Agalsidase alfa				
Changes in globotriaosylceramide (Gb_3) concentration in plasma Follow up: 6 months (umol/l)	The mean in changes in Gb_3 concentration in plasma score ranged between 0.63 and 10.19 umol/l	The mean in changes in Gb_3 concentration in plasma score in the intervention group was on average 2.07 fewer (6.64 fewer to 2.50 more) umol/l	NA	39 *2 studies*	⊕⊝⊝⊝ **very low** [1,2,3]	We found no statistically significant differences between studied groups in changes from baseline for $Gb_3$for which data were available.
Death	Outcome not reported	Outcome not reported.	Not estimable	NA	NA	
Pain **The Brief Pain Inventory severity** Follow up: over 5 months and up to 6 months	The mean for change in pain by the BPI severity was 4.7 (SD 2.25)	The mean for changes in pain by the BPI severity in the intervention group was on average 2.00 fewer (3.66 fewer to 0.34 fewer)	NA	26 *1 study*	⊕⊕⊝⊝ **low** [4]	We found a statistically significant differences favouring agalsidase alfa compared to placebo in pain for which data were available.
Renal function by creatinine clearance Follow up: at up to 6 months (mg/dL)	The mean in changes in renal function was 84.5 (SD: 35.15) mg/dL	The mean for changes in renal function in the intervention group was on average 10.30 more (15.37 fewer to 35.97 more) mg/dL	NA	24 *1 study*	⊕⊝⊝⊝ **very low** [2,4]	We found no statistically significant differences between studied groups in renal function for which data were available.

Symptoms and complications of disease:cardiac events	Outcome not reported.	Outcome not reported.	Not estimable	NA	NA
Symptoms and complications of disease: cerebrovascular events	Outcome not reported.	Outcome not reported.	Not estimable	NA	NA

*The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% CI) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).
CI: confidence interval; **RR**: risk ratio; **NA**: not applicable; **SD**: standard deviation

GRADE Working Group grades of evidence
High quality: further research is very unlikely to change our confidence in the estimate of effect.
Moderate quality: further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low quality: further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low quality: we are very uncertain about the estimate.

1. We downgraded the quality of evidence by 1 for high risk due to conflict of interest in one trial.
2. We downgraded the quality of evidence by 1 due to imprecision.
3. We downgraded the quality of evidence by 1 due to inconsistency.
4. We downgraded the quality of evidence by 2 due to only one single study reporting this outcome (lack of statistical power).

Summary of findings 2.

Enzyme replacement therapy for Anderson-Fabry disease

Patient or population: Anderson-Fabry disease

Settings: outpatients

Intervention: agalsidase beta

Comparison: placebo

Outcomes	Illustrative comparative risks (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Placebo	Agalsidase beta				

Changes in globotriaosylceramide (Gb_3) concentration in plasma Follow up: up to 18 months (umol/l)	The mean in changes in Gb_3 concentration in plasma score was 5.5 (SD: 1.6) umol/l	The mean in changes in Gb_3 concentration in plasma score in the intervention group was on average 4.80 fewer (5.45 fewer to 4.15) umol/l; respectively.	NA	58 *1 study*	⊕⊖⊖⊖ **very low** [1,2]	A statistically significant improvement on agalsidade beta compared to placebo was observed also observed in the domains of kidney (mean difference -1.70, (95% CI -2.09 to -1.31)) and heart (mean difference -0.90, 95% CI (-1.18 to -0.62)) .
Death Follow up: 18 months	0 per 1000	0 per 1000 (0 to 0)	1.85 (0.08 to 43.96)	82 *1 study*	⊕⊖⊖⊖ **very low** [1,2,3]	We found no statistically significant differences between studied groups in death which data were available.
Pain	Outcome not reported.	Outcome not reported.	Not estimable	NA	NA	
Renal function events (ITT population) Follow up: 18 months	225 per 1000	195 (83 to 459)	0.87 (0.37 to 2.04)	82 *1 study*	⊕⊖⊖⊖ **very low** [1,2,3]	We found no statistically significant differences between studied groups in renal function events which data were available.
Symptoms and complications of disease: cardiac events Follow up: up to 18 months	129 per 1000	59 (14 to 245)	0.46 (0.11 to 1.90)	82 *1 study*	⊕⊖⊖⊖ **very low** [1,2,3]	We found no statistically significant differences between studied groups in cardiac events which data were available.
Symptoms and complications of disease: cerebrovascular events (ITT population) Follow up: 18 months	64 per 1000	7 (1 to 158)	0.12 (0.01 to 2.48)	82 *1 study*	⊕⊖⊖⊖ **very low** [1,2,3]	We found no statistically significant differences between studied groups in cerebrovascular events which data were available.

*The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% CI) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).
CI: confidence interval; **RR**: risk ratio; **NA**: not applicable; **SD**: standard deviation.

GRADE Working Group grades of evidence
High quality: further research is very unlikely to change our confidence in the estimate of effect.
Moderate quality: further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low quality: further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.

Very low quality: we are very uncertain about the estimate.

1. We downgraded the quality of evidence by 1 for high risk due to conflict of interest.
2. We downgraded the quality of evidence by 1 due to only one single study reporting this outcome (lack of statistical power).
3. We downgraded the quality of evidence by 1 due to imprecision.

Summary of findings 3.

Enzyme replacement therapy for Anderson-Fabry disease

Patient or population: Anderson-Fabry disease

Settings: outpatients

Intervention: agalsidase alfa

Comparison: agalsidase beta

Outcomes	Illustrative comparative risks (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Agalsidase alfa	Agalsidase beta				
Changes in globotriaosylceramide (Gb_3) concentration in plasma and tissue Follow up: 12 months	Outcome not reported	Outcome not reported	Not estimable	NA	NA	
Death Follow up: not reported	0 per 1000	0 (0 to 0)	3.00 (0.13 to 69.09)	36 *1 study*	⊕⊖⊖⊖ **very low** [1,2,3]	We found no statistically significant differences between studied groups in death which data were available.
Pain Acroparaesthesia and Fabry crises Follow up: not reported	Outcome not reported	Outcome not reported	Not estimable	NA	NA	
Renal function	Outcome not reported	Outcome not reported	Not estimable	NA	NA	

Follow up: up to 24 months.						
Symptoms and complications of disease: cardiac events Follow up: not reported	142 per 1000	66 (7 to 653)	0.47 (CI 0.05 to 4.60)	29 *1 study*	⊕⊖⊖⊖ **very low** [1,2,3]	We found no statistically significant differences between studied groups in death which data were available.
Symptoms and complications of disease: cerebrovascular events Follow up: median 23.0 months	Outcome not reported.	Outcome not reported.	Not estimable.	NA	NA	

*The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% CI) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).
CI: confidence interval; **RR:** risk ratio; **NA**: not applicable.

GRADE Working Group grades of evidence
High quality: further research is very unlikely to change our confidence in the estimate of effect.
Moderate quality: further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low quality: further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low quality: we are very uncertain about the estimate.

1. We downgraded the quality of evidence by 1 for high risk due to lack of blinding, incomplete outcome data and, selective reporting.
2. We downgraded the quality of evidence by 1 due to only one single study reporting this outcome (lack of statistical power).
3. We downgraded the quality of evidence by 1 due to imprecision.

BACKGROUND

Please see glossary in the appendices for definition of terms used throughout the review (Appendix 1).

This is a second update of a Cochrane review first published in *The Cochrane Library* in 2010 (El Dib 2010), which included five studies that did not provide evidence on patient-important outcome measures. The first update of this review was then published in 2013 (El Dib 2013), which included only one new study and no information was changed. For this current version, a further three clinical trials not previously reviewed were included but they did not significantly alter the conclusions.

Description of the condition

Anderson-Fabry disease (AFD) is an X-linked, multi-system disorder caused by a deficiency of the lysosomal enzyme alpha–galactosidase A (AGAL). The incidence of AFD is estimated at 1 in 117,000 live births for males (Meikle 1999); although recent newborn screening surveys suggest the incidence may be much higher, up to 1 in 3,100 (Spada 2006). One reasonable explanation for this difference in the incidence of AFD between these studies is that the first (Meikle 1999) refers to the incidence of classic AFD while the latter (Spada 2006) refers to the full phenotypic spectrum reflecting the expansion in phenotypic variation identified in the last decade.Variants include those with sole involvement of the heart, kidneys or brain. For instance, the renal variant was first described in 2003. Although the vast majority of reports have focused on symptomatic males, females with AFD can develop disease-related problems (Wilcox 2008).

Clinically, AFD is characterized by major renal, cardiac and cerebrovascular complications consequent to the progressive deposition of incompletely metabolized glycosphingolipids, mainly globotrysilceramide (Gb_3) in multiple cell types. The precise mechanism of tissue injury remains unclear though alterations in vascular reactivity and a propensity for thrombo-embolic disease are believed to play a role in the increased risk for particular problems, such as stroke. Gb3 has been used as a biomarker in AFD being measured in plasma and urine by tandem mass spectrometry. The reference ranges for plasma and urinary Gb3 levels are 5.6 (3.6-7.5) µg/ml and 0.016 (0.01 - 0.03) mg/mmol of creatinine respectively. Gb3 levels are consistently elevated in most people with AFD and decrease after treatment initiation with ERT. Thus, it has been proposed to consider Gb3 levels as part of the diagnostic process as well as a biomarker of response to ERT. This said, the reliability of Gb3 levels as a surrogate marker of disease severity and of treatment response has been questioned by some investigators (Young 2005). Recently studies have shown that a deacylated form of Gb_3 (globotriaosylsphingosine, lyso-Gb_3) is elevated in plasma obtained from individuals with AFD. Lyso-Gb_3 is a potent inhibitor of AGAL and alpha–galactosidase B (N-acetylgalactosaminidase), and it has been found to promote smooth muscle cell proliferation in vitro (Aerts 2008). Furthermore, it has been suggested lyso-Gb3 may identify the agalA mutations leading to classic Fabry disease (Niemann 2014).

Renal and cardiac failure represent major sources of morbidity, and account for the reduced survival among affected males and females compared to the normal population (median age of death is 50 to 57 years and 70 to 72 years, respectively). The pain crises, acroparaesthesia, hearing loss and gastrointestinal problems experienced lead to significant reduction in health-related quality of life. While the majority of reports focus on males, females with AFD can develop disease-related problems. Clinical expression among females tends to be more variable and onset of symptoms tends to occur at a later age. The expression of the disease in females appears to be influenced by the particular *AGAL* mutation and the pattern of X chromosome inactivation in each organ (Niemann 2014; Wang 2007).

Description of the intervention

Enzyme replacement therapy (ERT) for AFD consists of the regular intravenous infusion of a recombinant enzyme formulation. Two forms of recombinant AGAL exist; agalsidase alfa (Replagal™), Shire Human Genetic Therapies, Cambridge, MA) and agalsidase beta (Fabrazyme®, Genzyme Corporation, Cambridge, MA). Agalsidase alfa is generated by the activation of the AGAL gene in a continuous human cell line; whereas agalsidase beta is produced in a Chinese hamster ovary (CHO) mammalian cell expression system transduced with the human AGAL sequence. Both enzyme preparations are approved in Europe and many other countries, but in the United States the Federal Drug Administration approved only agalsidase beta (Eng 2001; Schiffmann 2001). Administration of ERT is usually once every two weeks, using a dose of 0.2 mg/kg body weight when using agalsidase alfa or 1 mg/kg for agalsidase beta.

Intravenous enzyme infusions appear to be reasonably well tolerated, with reported infusion reactions of about 10%; mostly consisting of fever and transient rigours of mild to moderate intensity. A proportion of people with AFD receiving ERT have sero-converted (i.e. developed antibodies); the frequency of antibodies against agalsidase alfa and agalsidase beta has been reported at 55% and 83% of individuals treated respectively (Eng 2001; Schiffmann 2001). Antibody formation did not influence clinical efficacy or outcomes in either of the initial clinical studies undertaken, and antibody titres usually decreased over time. In a few cases, IgE antibodies have been reported after infusion of agalsidase beta (Eng 2001). Recent studies have shown the presence of antibodies may influence the Gb_3 storage in skin capillaries and Gb_3 excretion in urine, although no relation between antibody formation and plasma Gb_3 levels or clinical outcome has been established thus far (Hollack 2009).

How the intervention might work

Treatment of Fabry disease consists of symptom management and replacement of the deficient or dysfunctional enzyme with enzyme replacement therapy. ERT supplies the organs with recombinant enzyme and therefore reduces the amount of Gb3 accumulation in tissues with consecutive multisystem damage. ERT is available since 2001, in the form of two recombinant GLA preparations: agalsidase alfa (Replagal, Shire Human Genetic Therapies, Cambridge, MA, 0.2 mg/kg per infusion), and agalsidase beta (Fabrazyme, Genzyme Corporation, Cambridge, MA, 1 mg/kg per infusion). ERT is administered intravenously either through a peripheral line or central access device, infusions typically occur once every two weeks.

Why it is important to do this review

A systematic review is needed to establish the evidence base for the effectiveness and safety of ERT for treating AFD. This review is of

particular relevance since ERT has now been available for almost 15 years and a review of the most recent data may provide more guidance in its use.

This is an update of a Cochrane review first published in 2010, and previously updated in 2013 (El Dib 2010; El Dib 2013).

OBJECTIVES

To evaluate the effectiveness and safety of ERT compared to other interventions, placebo or no interventions for treating AFD.

METHODS

Criteria for considering studies for this review

Types of studies

Randomized and quasi-randomized controlled clinical trials.

Types of participants

Individuals with AFD of any age and any degree of disease severity. Diagnosis should be established either by accepted criteria based on concentration of enzyme activity or by mutation analysis.

Types of interventions

Enzyme replacement therapy (agalsidase beta or agalsidase alfa) in any amount given for a period of at least one month compared to: each other; another intervention (fat-restricted diet, drugs, exercises, etc); no intervention; or to placebo.

Types of outcome measures

Primary outcomes

1. Changes in globotriaosylceramide (Gb_3) concentration in plasma and tissue (i.e. endothelial cells)
2. All-cause death
3. Pain (measured by the McGill Pain Questionnaire*)
   a. Acroparaesthesia (measured by the intensity and duration of acroparaesthesia as reported by the individual)
   b. Fabry crises

**Post hoc* change: we also considered other validated pain questionnaires.

Secondary outcomes

1. Effect of therapy on renal function (e.g. reduction in serum creatinine and proteinuria; creatinine and inulin clearance)
2. Symptoms and complications of disease such as occurrence of renal failure, skin, cerebrovascular and cardiac complications based on the following observations: serum creatinine level, proteinuria (ratio of urinary protein to urinary creatinine in mg/dL), 12-lead electrocardiography, echocardiography parameters (such as thickness of cardiac structures, left ventricular volume, measures of systolic and diastolic function, heart rate), neurologic examination, head magnetic resonance imaging, exercise tolerance, and AFD symptom assessment
3. Histologic analysis of microvascular capillary endothelial deposits of Gb_3 in biopsy specimens
4. Adverse effects of treatment (including severe adverse effects such as dyspnoea, malaise, hypertension and gastrointestinal symptoms, and antibody formation), based on the type and frequency of adverse events in treated participants and those on placebo.
5. Quality of life (QoL) (as determined by the Short Form 36 (SF-36) and the impact of clinical variables on domain scores within the SF-36* (Smith 2000).

**Post hoc* change: we also considered other validated QoL questionnaires.

Search methods for identification of studies

There was no language restriction and the trials were identified from the sources listed below.

Electronic searches

Relevant trials were identified from the Cystic Fibrosis and Genetic Disorders Group's Inborn Errors of Metabolism Trials Register using the term: fabry disease.

The Register is compiled from electronic searches of the Cochrane Central Register of Controlled Trials (CENTRAL) (updated with each new issue of *The Cochrane Library*), weekly searches of MEDLINE and the prospective handsearching of one journal - *Journal of Inherited Metabolic Disease*. Unpublished work were identified by searching through the abstract books of the Society for the Study of Inborn Errors of Metabolism conference and the SHS Inborn Error Review Series. For full details of all searching activities for the register, please see the relevant section of the Cystic Fibrosis and Genetic Disorders Group Module.

Date of the most recent search of the Cystic Fibrosis and Genetic Disorders Group's Inborn Errors of Metabolism Trials Register: 08 July 2016.

We also searched Cochrane Central Register of Controlled Trials (CENTRAL) (Issue 9, 2015, www.cochranelibrary.com) Ovid Embase (1980 to 24 September 2015), PubMed (1980 to 24 September 2015; www.ncbi.nlm.nih.gov/pubmed) and the Literature Latino-Americana e do Caribe em Ciências da Saúde - LILACS (1982 to 24 September 2015; http://lilacs.bvsalud.org). These search strategies are listed in the appendices (Appendix 2; Appendix 3; Appendix 4; Appendix 5).

Searching other resources

Reference lists of the identified relevant trials were scrutinized for additional citations.

Specialists in the field and authors of the included trials were contacted for any possible unpublished data.

We also searched the abstract books of WORLD LDN.

Data collection and analysis

Selection of studies

Two authors (RED and HG) independently screened the trials identified. Discrepancies were resolved by discussion.

Data extraction and management

Two authors (RED and HG) independently extracted data and discrepancies were resolved by discussion. We used a standard

form to extract the following information: characteristics of the trial (design, methods of randomisation), participants, interventions and outcomes (types of outcome measures, timing of outcomes, adverse events).

We presented different enzyme therapies (alfa and beta) as well as different control groups (placebo or active controls) as separate interventions as we did not judge these sufficiently comparable to combine.

When possible, outcome data were grouped into those measured at up to one month, over one month and up to three months, over three months and up to six months and over six months and up to 12 months and annually thereafter. In a *post hoc* change, we also considered other time points such as 'over five months and up to six months' where multiple data sets from an individual trial were available for a single planned time point.

Assessment of risk of bias in included studies

We assessed every trial using a simple form and followed the domain-based evaluation as described in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011).

We assessed the following domains as having either low, unclear or high risk of bias:

1. randomisation
2. concealment of allocation
3. blinding (of participants, caregivers and outcome assessors)
4. incomplete outcome data
5. selective reporting
6. other potential sources of bias

1. Randomisation

Low risk: adequate generation of allocation
Unclear risk: not described in the paper or by contacting authors
High risk: inadequate generation of allocation

2. Concealment of allocation

Low risk: adequate allocation concealment
Unclear risk: not described in the paper or by contacting authors
High risk: inadequate allocation concealment

3. Blinding (of participants, caregivers and outcome assessors)

Low risk: adequately described; adequate method
Unclear risk: described as blinded, but no information provided
High risk: not blinded; inadequate method

If a trial measured an objective outcome then lack of blinding was rated as low risk of bias.

4. Incomplete outcome data

We recorded the rates of withdrawal for each outcome as follows.
Low risk: less than 20% and equal for both groups;
Unclear risk: not reported in paper or by authors;
High risk: greater than 20% or not equal for any comparison groups or both.

5. Selective reporting

We considered the possibility of selective reporting of outcomes when data were not available in the 'Results' section of the published paper, but according to the 'Methods' section these outcome data were collected.

6. Other potential sources of bias

We recorded any other factors we felt might cause bias.

Measures of treatment effect

For dichotomous data (such as death, presence or absence of Fabry crises and adverse effects), we used the risk ratio (RR), with 95% confidence intervals (95% CIs) as the effect measure.

For continuous data (such as changes in Gb_3 concentration, echocardiographic parameters, pain and quality of life scores) we used the mean difference (MD) (in which the effect estimates of individual trials are weighted by dispersion measures), with 95% CIs. When standard errors (SE) were reported within the trial reports, we converted these to standard deviations (SD) (SD = SE x square root of n). For future updates of this review we plan to use standardized mean difference (SDM).

For time-to-event data (such as effects on renal function) we planned to consider a joint model for longitudinal and discrete time-to-event data in which the discrete event time distribution is modelled as a linear function of the slope of an individual's longitudinal process on the probit scale (Jones 2009). Effect of therapy on renal function (e.g. increase in serum creatinine and proteinuria; creatinine and inulin clearance) could be measured as time-to-event-data or number of events. However, the only trial reporting on this outcome only reported on one time point, which has been presented as continuous data (Schiffmann 2001).

Unit of analysis issues

We have included data from an eligible cross-over trial and analysed this according to a method recommended by Elbourne, whereby we inserted the mean and SD of the participant-specific differences between the intervention and control measurements taking all these measurements from intervention periods and all measurements from control periods and, we analysed these as if the trial was a parallel group trial of intervention versus control group (Elbourne 2002). We appreciate that this is a conservative method and will overestimate the SE of the MD by treating (paired) within differences as independent data.

Dealing with missing data

For any new trial which may be included in a future update of this review, we will contact authors, as necessary, to clarify methodological issues (such as generation and allocation concealment, blind method and withdrawals) as well as for any missing outcome data.

Assessment of heterogeneity

We planned to qualify inconsistency among the pooled estimates using the I^2 statistic. This illustrates the percentage of the variability in effect estimates resulting from heterogeneity rather than sampling error (Higgins 2003; Higgins 2011). We considered there to be a low degree of heterogeneity if I^2 was below 25%, a

moderate degree if I^2 between 25% and 50%, and a high degree if I^2 was over 50%.

Assessment of reporting biases

We planned to assess publication bias by drawing a funnel plot (trial effect versus trial size), but there were not sufficient trials included in the review. In future analysis, funnel plots will be used in an exploratory data analysis to assess for the potential existence of small trial bias. There are a number of explanations for the asymmetry of a funnel plot, including true heterogeneity of effect with respect to trial size, poor methodological design of small trials (Sterne 2001) and publication bias and selective reporting of outcomes. Thus, this exploratory data tool may be misleading (Tang 2000; Thornton 2000) and we will not place undue emphasis on this tool.

Data synthesis

We used the fixed-effect model to analyse data, if in future updates, significant heterogeneity (e.g. I^2 higher than 50%) is identified, we will compute pooled estimates of the treatment effect for each outcome under a random-effects model (with two or more trials).

Subgroup analysis and investigation of heterogeneity

For future reviews (including 10 or more trials) we plan to investigate heterogeneity by conducting meta-analyses by subgroups as described below.

1. Dose. We plan to sub-divide dose in to lower dose (less than 0.2 mg/kg) and higher dose (more than 0.2 mg/kg). These cut off doses were chosen arbitrarily.
2. Duration of intervention. We plan to sub-divide duration of intervention up to one year and more than one year. These time divisions were chosen arbitrarily.
3. Age at commencement of treatment, for example, up to the age of 18 years and over age 18 years.
4. Severity of disease as stratified into less severe and more severe (as reported within the trials).

Sensitivity analysis

If we had included an adequate number of trials, we planned to perform a sensitivity analysis to test the robustness of analyses to certain assumptions in the results. In future analysis, we will include the following factors in the sensitivity analysis, separating trials according to:

1. allocation concealment quality (low risk, high risk or unclear risk);
2. blinding of participants, caregiver and outcome assessment (low risk, high risk or unclear risk);
3. rates of withdrawal for each outcome.

Summary of findings tables

In our review, we used the principles of the GRADE (Grades of Recommendation, Assessment, Development and Evaluation) system (Guyatt 2008) to assess the quality of the body of evidence associated with specific outcomes (changes in globotriaosylceramide (Gb_3) concentration in plasma and tissue; death; pain; renal function; and symptoms and complications of disease (i.e., cardiac and cerebrovascular events)) and constructed a summary of findings (SoF) table using GRADE software. The GRADE approach appraises the quality of a body of evidence according to the extent to which one can be confident that an estimate of effect or association reflects the item being assessed. Assessment of the quality of a body of evidence considers within-trial risk of bias (methodological quality), directness of the evidence, heterogeneity of the data, precision of effect estimates and risk of publication bias. The quality of the evidence for a specific outcome will be altered by a level according to the performance of trials against these five factors.

High-quality evidence: findings are consistent among at least 75% of RCTs with low risk of bias; data are consistent, direct and precise, and no publication biases are known or suspected. Further research is unlikely to change the estimate or our confidence in the results.

Moderate-quality evidence: one of the domains is not met. Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.

Low-quality evidence: two of the domains are not met. Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.

Very low-quality evidence: three of the domains are not met. We are very uncertain about the results.

No evidence: no RCTs that addressed this outcome were identified.

RESULTS

Description of studies

See: Characteristics of included studies; Characteristics of excluded studies.

Results of the search

For the original review, we identified 273 references from the electronic searches (El Dib 2010). After initial assessment of these references, 56 were looked at in more detail. A total of 31 were excluded from the review (Excluded studies). Thus, five trials (Banikazemi 2007; Bierer 2006; Hughes 2008; Schiffmann 2001; Eng 2001) (represented by 25 individual references), which enrolled 187 participants were included (Included studies).

For the first update of the review in 2012, 368 references were identified by the searches. After an initial assessment seven references were considered. Of these we included one new trial (Vedder 2007) (represented by five individual references) and, excluded two further trials (Fernhoff 2011; West 2011).

For the second update of the review in 2016, 19 references were identified. We selected all references for careful consideration and obtained them in full text, where available. Following assessment of the full articles, we included three new clinical trials (Clarke 2007; Hughes 2013; Sirrs 2014) (represented by four individual references) and, we excluded 12 further studies (Benjamin 2014; Fellgiebel 2014; Germain 2013; Hughes 2014; Kim 2014; Rombach 2012; Schiffmann 2013; Schiffmann 2014; Sirrs 2011; Tøndel 2013; Tsuboi 2014; Weidemann 2014). One further trial is currently listed in 'Studies awaiting classification' (represented by three individual references) and will be fully assessed in the next update of this review (Wijburg 2015).

Therefore, for this second update we have a total of nine included trials (Banikazemi 2007; Bierer 2006; Clarke 2007; Eng 2001; Hughes 2008; Hughes 2013; Schiffmann 2001; Sirrs 2014; Vedder 2007) (represented by 34 individual references) (Included studies) involving a total of 351 participants (Figure 1), 43 excluded trials (Excluded studies) and three trials awaiting assessment (Benjamin 2014; Hughes 2014; Wijburg 2015).

Figure 1. Study flow diagram for the second update.

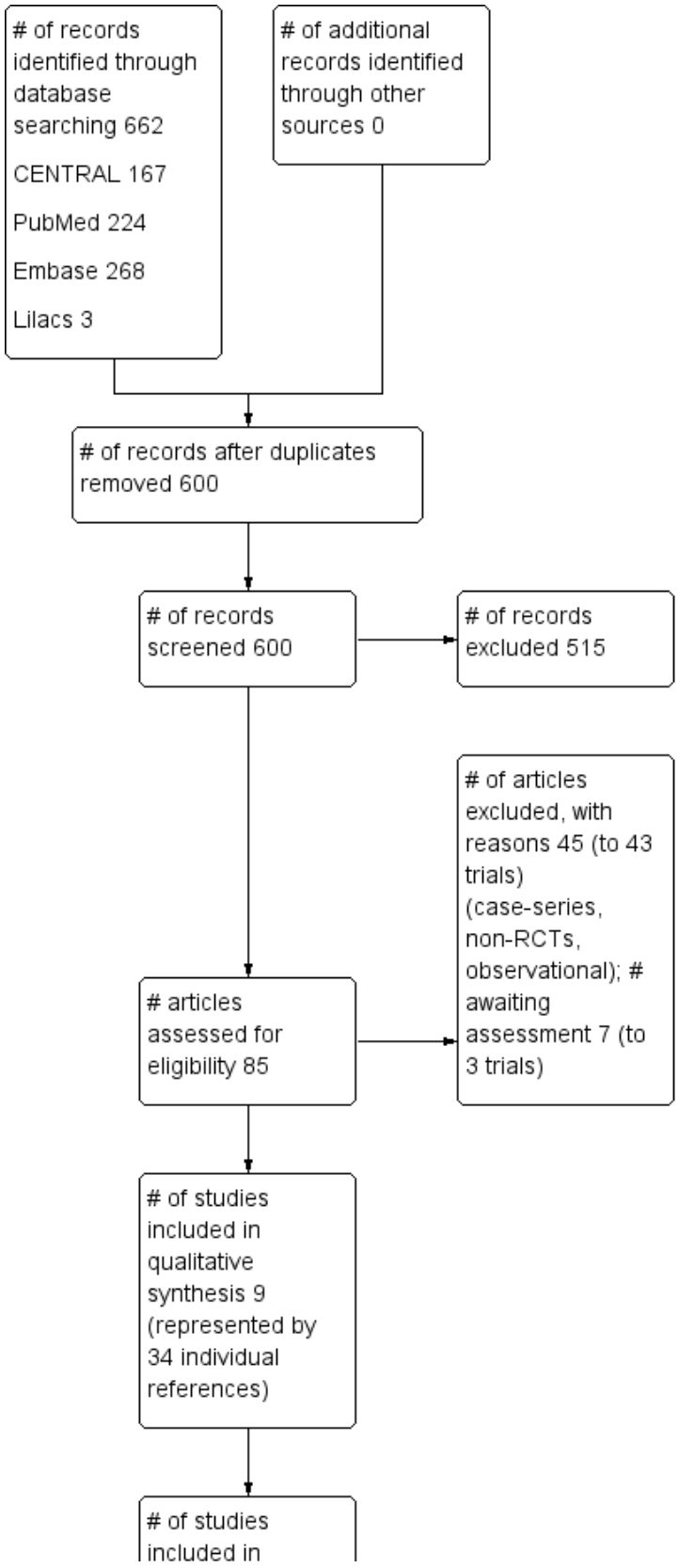
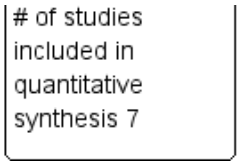


Figure 1. (Continued)



Included studies

Agalsidase alfa versus placebo

Two trials (n = 41) were included in this comparison and are described in detail below (Hughes 2008; Schiffmann 2001).

Trial design

Both trials were described as randomized, double-blind, placebo-controlled, clinical trials (Hughes 2008; Schiffmann 2001). Both trials were for six months (Hughes 2008; Schiffmann 2001), but one had an additional 24 months open-label follow up (Hughes 2008).

Both trials recruited only males and included 15 and 26 participants respectively (Hughes 2008; Schiffmann 2001). The ratio of participants in the treatment and placebo groups varied; the Schiffmann trial achieved an almost equal split, randomising 14 participants to treatment and 12 to placebo (Schiffmann 2001); and in the Hughes trial seven and eight participants were randomised to the treatment and to the placebo groups respectively (Hughes 2008).

Types of interventions

Both trials compared ERT to placebo and used the same dose regime of Agalsidase alfa (Replagal™) administered intravenously at a dose of 0.2 mg/kg over a period of 20 or 40 minutes for six months. The treatment regimen was the same for the additional 24-month open-label follow up (Hughes 2008).

Types of outcomes measured

Moore (in a report of the Schiffmann trial) evaluated transversal doppler measurements, left ventricular volume, heart rate and stroke volume. The following Doppler parameters were obtained: peak flow velocity, mean flow velocity, end-diastolic velocity, pulsatility index, and resistance index (Schiffmann 2001).

At baseline and six months, left ventricular mass assessed by magnetic resonance imaging (MRI), QRS duration, levels of Gb3 in cardiac tissue, urine sediment and plasma, and adverse effects were evaluated in the Hughes trial (Hughes 2008).

Agalsidase beta versus placebo

Three trials (n = 146) were included in this comparison and are described in detail below (Banikazemi 2007; Bierer 2006; Eng 2001).

Trial design

All three trials were described as randomized, placebo-controlled, clinical trials (Banikazemi 2007; Bierer 2006; Eng 2001); and two of these were described as double blind (Banikazemi 2007; Eng 2001). Trial duration ranged from five (Eng 2001) to 35 months (Banikazemi 2007).

The number of participants included in each trial ranged from six (Bierer 2006) to 82 (Banikazemi 2007) and the three trials randomized mostly males (Banikazemi 2007; Bierer 2006; Eng 2001). The ratio of participants in the treatment and placebo groups varied across trials; two had a ratio of 2:1 treatment-to-placebo (Banikazemi 2007; Bierer 2006); and one had an even split of 29 participants in each group (Eng 2001).

In one trial, the investigators were part of the Genzyme Corporation in Cambridge, Massachussetts (Eng 2001). Only one trial was described as multicenter; with there being 26 referral centers from six countries from North America and Europe (Banikazemi 2007).

Types of interventions

All three trials compared ERT - agalsidase beta (recombinant human alfa-galactosidase A) - to placebo (Banikazemi 2007; Bierer 2006; Eng 2001). The treatment regimen was the same in these trials with Agalsidase beta administered at a dose of 1mg/kg intravenously every two weeks. Duration of the treatment varied from 20 weeks (Eng 2001), to 35 months (median 18.5 months) (Banikazemi 2007), and 18 months (Bierer 2006).

Types of outcomes measured

Thurberg (in a report of the Eng trial) evaluated urinary creatinine, urinary protein excretion, renal function and dermatologic characteristics of Gb3 accumulation in the dermis (Eng 2001). Measurements were taken at baseline and after infusion 11 at five months.

Banikazemi measured the time to first clinical event (renal, cardiac, cerebrovascular event or death) (Banikazemi 2007). The following measures were taken: serum creatinine level, proteinuria (ratio of urinary albumin to urinary creatinine), 12-lead electrocardiography, echocardiography, neurologic examination, head MRI, Brief Pain Inventory, exercise tolerance, plasma Gb3 level, Fabry symptom assessment, physical examination, blood chemistry, urinalysis, IgG antibody titers to agalsidase beta and optional skin biopsy. All measurements were taken at baseline. Serum creatinine levels were measured every four weeks aechocardiography, head MRI, and exercise tolerance,were repeated every 24 weeks and all other baseline measurements were repeated every 12 weeks. The estimated glomerular filtration rate (GFR) was determined by using the 4-variable Modification of Diet in Renal Disease formula.

Bierer measured cardiopulmonary exercise performance, forced expiratory volume and forced vital capacity every three months over an 18-month period (Bierer 2006).

Agalsidase alfa versus agalsidase beta

Two trials (n = 184) were included in this comparison and are described in detail below (Sirrs 2014; Vedder 2007).

Trial design

The trial conducted by Vedder was a randomized clinical trial with participants being treated for a period of at least 12 months. A total of 36 participants (18 males and 18 females) were included. A total of 34 participants had at least 12 months of follow up and a subgroup of participants (25 out of 34) was followed up for more than 24 months of treatment. Two female participants withdrew after six months of agalsidase alfa or agalsidase beta treatment (Vedder 2007).

The Sirrs trial was a nationwide study of all individuals in Canada with Fabry disease between ages five and 85 years old. This trial looked at the two Canadian Fabry Disease Initiative (CFDI) cohorts of enzyme replacement (ERT) treated individuals. Cohort 1a: participants on ERT when the CFDI began who maintained their baseline treatment assignment (these participants were not randomised and therefore not included in the review). Cohort 1b: participants newly meeting criteria for ERT and randomized 1:1 to agalsidase beta (1.0 mg/kg every two weeks) or agalsidase alfa (0.2 mg/kg every two weeks). A total of 67 participants were randomized; mean follow up was at 23.00 months (Sirrs 2014).

Types of interventions

In one trial, participants were treated with either agalsidase alfa or agalsidase beta at an equal dose of 0.2 mg/kg bi-weekly (Vedder 2007). In the other trial participants were randomized 1:1 to agalsidase beta 1.0 mg/kg every two weeks or agalsidase alfa 0.2 mg/kg every two weeks (Sirrs 2014).

Types of outcomes measured

In the Vedder trial, reduction in left ventricular mass after 12 and 24 months of treatment was considered the primary outcome. The authors also evaluated the occurrence of treatment failure (defined as progression of cardiac, renal or cerebral disease), GFR, pain, anti-agalsidase antibodies and GL3 levels in plasma and urine (Vedder 2007).

In the Sirrs trial comparison was made between the effects of agalsidase alfa and agalsidase beta on a composite clinical outcome consisting of renal (dialysis, transplant, or reduction in GFR by 50%), cardiac (admission for cardiac event), neurologic (stroke or sudden unilateral hearing loss) or death (Sirrs 2014).

Multiple agalsidase alfa dosing schedules

Two trials (n = 36) were included in this comparison and are described in detail below (Clarke 2007; Hughes 2013).

Trial design

Both trials were described as randomized, double-blind, placebo controlled, clinical trials (Clarke 2007; Hughes 2013). One trial was 10 weeks in length (Clarke 2007), while the other was four weeks (Hughes 2013). Each trial recruited 18 participants all of whom were male in one trial (Clarke 2007), while in the other participants of both genders were included (12 males and 6 females). One trial was a cross-over design where all participants received the same interventions sequentially (Hughes 2013). The other achieved an almost equal split between five arms (Clarke 2007).

Types of interventions

Both trials compared ERT at different dosage regimens. The Hughes trial used three treatment schedules: treatment A 0.2 mg/kg every other week; treatment B, 0.1 mg/kg weekly and treatment C, 0.2 mg/kg weekly (Hughes 2013). The Clarke trial compared five different dosage regimens of agalsidase alfa: 0.1, 0.2, or 0.4 mg/kg weekly; 0.2 mg/kg every other week (the approved dose) or 0.4 mg/kg every other week (Clarke 2007).

Types of outcomes measured

For the Hughes trial, the primary outcome variable was self-assessed health state measured by the visual analogue scale ('thermometer') item of the European quality of life questionnaire (the EQ-5D: Euroqol Group 1990).

Secondary outcome variables were:

1. pain as assessed as the average composite pain severity dimension of the brief pain inventory (BPI) short form, a standard pain assessment tool, each individual item of the BPI short form, health state as calculated from items 1–5 of the EQ-5D questionnaire (mobility, self-care, usual activities, pain/discomfort, and anxiety/depression), each individual item of the EQ-5D questionnaire;
2. results of quantitative sudomotor axon reflex test (QSART) testing which tests for abnormalities of resting and evoked sweat production;
3. the Mainz severity score index (MSSI), a scoring system to measure the severity of Fabry disease;
4. plasma and urine Gb3; and
5. analgesic use.

All questionnaire-based data were completed by the participant on a daily diary sheet (health state, pain and analgesic use) and using weekly investigator administered questionnaires (BPI and EQ-5D). Safety assessments included physical examination, 12-lead ECG, clinical laboratory testing, and vital sign measurements. Adverse events (AEs) and concomitant medications were recorded throughout the trial. Anti-agalsidase alfa antibodies were assayed at baseline using an enzyme-linked immunosorbent assay (ELISA) (Hughes 2013).

The primary efficacy endpoint variable for the Clarke trial was change in plasma Gb3 level from baseline to the day of the final infusion (Clarke 2007).

Excluded studies

A total of 43 studies were excluded from the review (Alamartine 2005; Banikasemi 2005; Beck 2004; Beer 2006; Breunig 2006; Cartwright 2004; Elliott 2006; Eto 2005; Fellgiebel 2014; Fernhoff 2011; Germain 2007; Guffon 2002; Guffon 2004; Hajioff 2006; Hilz 2004; Jardim 2006; Jardim 2006b; Kalliokoshi 2006; Kampmann 2002; Kobayashi 2005; Kosch 2004; Linthorst 2004; Linthorst 2006; Mignani 2004; Mills 2004; Pisani 2005; Ramaswami 2007; Ries 2006; Schiffmann 2003; Schiffmann 2006; Schiffmann 2014; Sirrs 2011; Spinelli 2004; Tsuboi 2014; Utsumi 2005; Weidemann 2003; Weidemann 2014; West 2011). The main reasons for exclusion being that these were case series, cohort studies, retrospective studies or non-randomized trials.

Risk of bias in included studies

See: Figure 2; Figure 3 and Characteristics of included studies.

Figure 2. Risk of bias graph: review authors' judgements about each risk of bias item presented as percentages across all included studies.

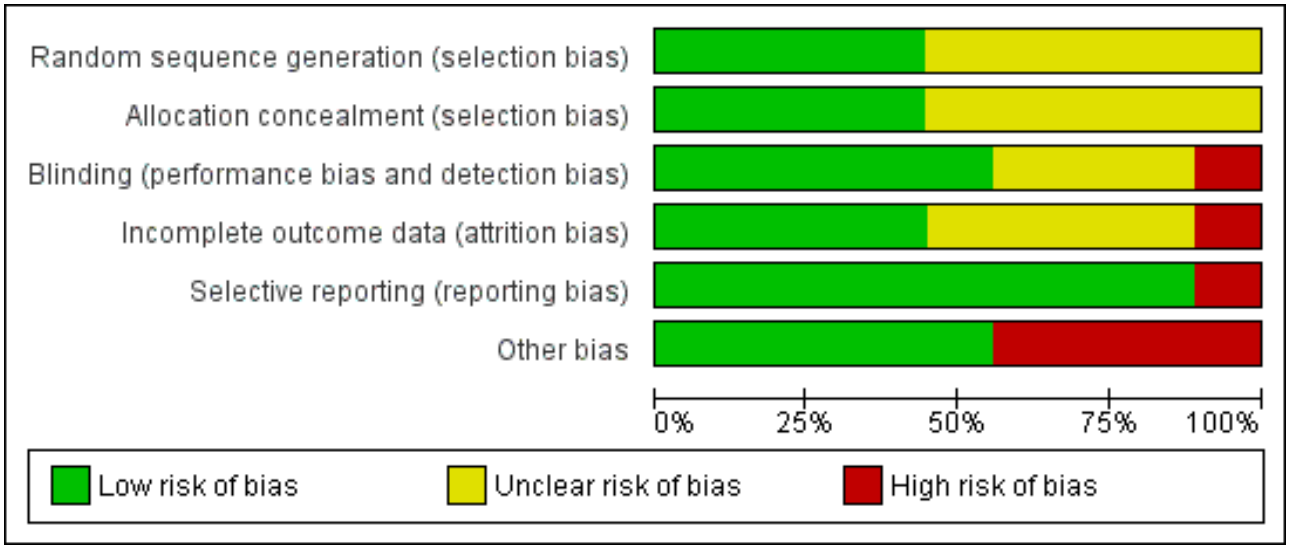
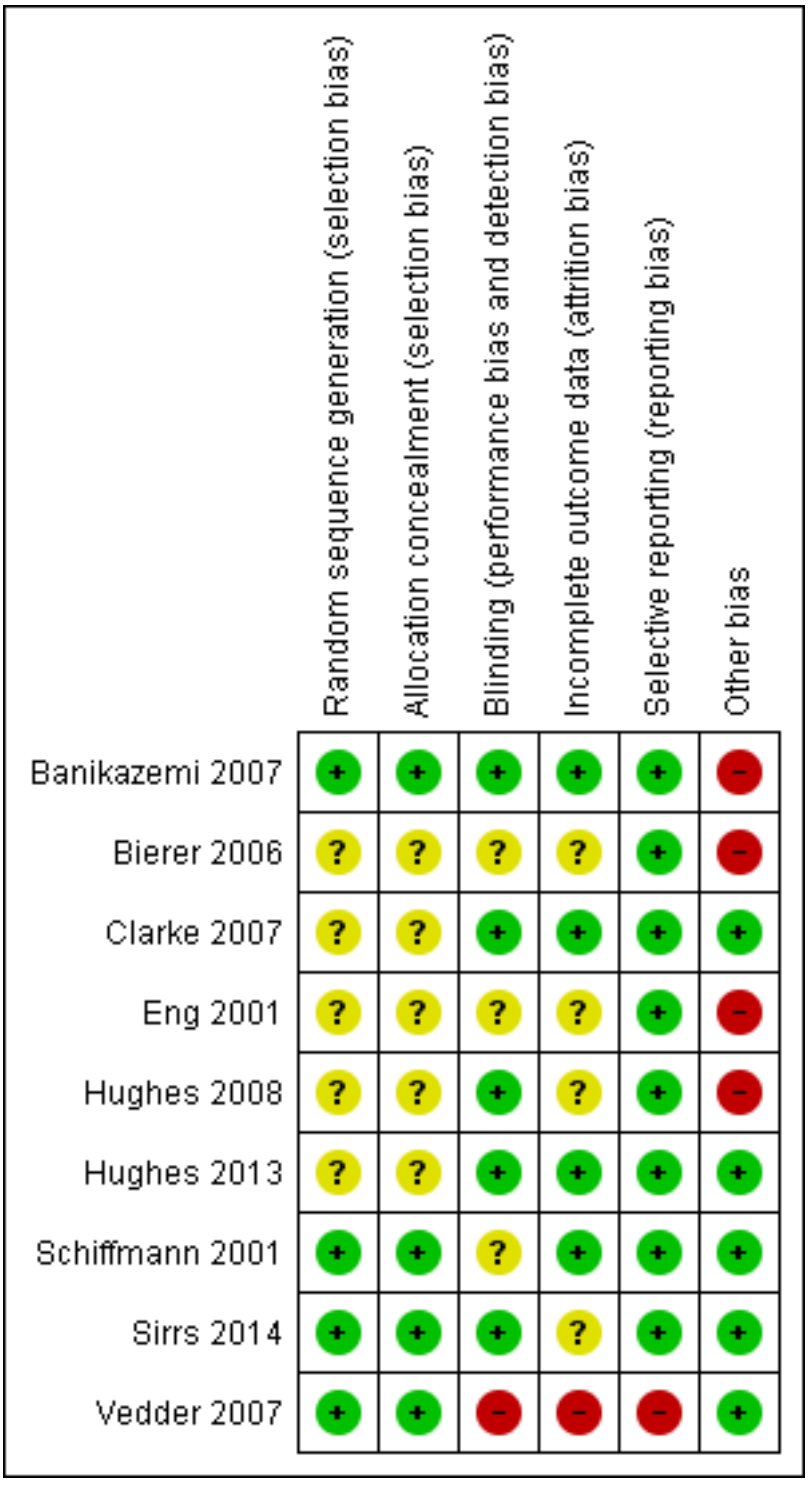


Figure 3. Risk of bias summary: review authors' judgements about each risk of bias item for each included study.



Agalsidase alfa versus placebo

Generation of randomization sequence

The Hughes trial did not describe the generation of allocation, thus, this trial was classified as having an unclear risk of bias (Hughes 2008). The Schiffmann trial reported the generation of allocation was made by random tables and, therefore we rated this trial as low risk of bias for this domain (Schiffmann 2001).

Allocation concealment

The Hughes trial did not describe the concealment of allocation so this was judged to have an unclear risk of bias (Hughes 2008). The Schiffmann trial reported that randomization was provided by an unblinded pharmacist and, therefore we rated this trial as low risk of bias for this domain (Schiffmann 2001).

Blinding

The Hughes trial reported data remained blinded until the database was unlocked and the statistical analyses performed (Hughes 2008). We therefore judge this to be at a low risk of bias regarding this domain. However, the Schiffmann trial did not describe any blinding process and, therefore it was classified as having an unclear risk of bias (Schiffmann 2001).

Incomplete outcome data

The Hughes trial did not describe withdrawals, dropouts or ITT, therefore we judged this to have an unclear risk of bias (Hughes 2008). The Schiffmann trial describes only four withdrawals and, therefore we rated this trial as low risk of bias for this domain (Schiffmann 2001).

Selective reporting

We judged both included trials to be free of selective reporting and having a low risk of bias (Hughes 2008; Schiffmann 2001).

Other potential sources of bias

We did not identify any other potential sources of bias (Hughes 2008; Schiffmann 2001).

Agalsidase beta versus placebo

Generation of randomization sequence

The Banikazemi trial described the generation of randomization as computer-generated and, therefore we rated this trial as low risk of bias (Banikazemi 2007).The Bierer and Eng trials did not describe details on how the sequences were generated; therefore these trials presented an unclear risk of bias (Bierer 2006; Eng 2001).

Allocation concealment

The Banikazemi trial was classified as having a low risk of bias since the randomization codes were maintained centrally at a secure location (Banikazemi 2007). The Bierer and Eng trials did not describe details regarding the concealment of allocation; thus, these trials were classified as having an unclear risk of bias (Bierer 2006; Eng 2001)

Blinding

The Banikazemi trial described that the sponsor staff, investigators, and participants were blinded to treatment allocation leading to a low risk of bias (Banikazemi 2007). The Bierer and Eng trials were described as double blind, but provided no further details, we therefore judge these two trials to have an unclear risk of bias (Bierer 2006; Eng 2001).

Incomplete outcome data

The Banikazemi trial reported less than 20% of withdrawals and dropouts, we therefore assessed this as having a low risk of bias (Banikazemi 2007). The Bierer and Eng trials did not describe withdrawals, dropouts or ITT, therefore we judged this to have an unclear risk of bias (Bierer 2006; Eng 2001).

Selective reporting

We judged all three included trials to be free of selective reporting (Banikazemi 2007; Bierer 2006; Eng 2001).

Other potential sources of bias

We judged all three included trials to be at high risk of bias as the investigators were part of the Genzyme Corporation (Banikazemi 2007; Bierer 2006; Eng 2001).

Agalsidase alfa versus agalsidase beta

Generation of randomization sequence

Both trials described the generation of randomization as manual randomization and, therefore we rated this domain as low risk of bias (Sirrs 2014; Vedder 2007).

Allocation concealment

The Vedder trial was classified as having a low risk of bias since the investigators used envelopes that were checked by two people not involved in obtaining informed consent, thus we classified the trial as having a low risk of bias (Vedder 2007). The Sirrs trial reported that a third party was involved in the generation of allocation; thus, this trial was classified as having a low risk of bias (Sirrs 2014).

Blinding

The Vedder trial was classified as having a high risk of bias since there was no blinding (Vedder 2007). The Sirrs trial was not blinded but the composite outcome consisting of renal, cardiac, neurologic and, death is unlikely to be affected by lack of blinding, hence it was judged to have low risk of bias (Sirrs 2014).

Incomplete outcome data

The Vedder trial reported more than 20% of withdrawals and dropouts, we therefore assessed this as having a high risk of bias (Vedder 2007). The Sirrs trial did not describe withdrawals, dropouts or ITT, therefore we judged this to have an unclear risk of bias (Sirrs 2014).

Selective reporting

he Vedder trial reported quality of life as an outcome in the protocol, but this was not stated in the paper, we therefore assessed this as having a high risk of bias (Vedder 2007). The Sirrs trial was free of selective reporting and, therefore we classified this domain as having a low risk of bias (Sirrs 2014).

Other potential sources of bias

We did not identify any other potential sources of bias (Vedder 2007; Sirrs 2014).

Agalsidase alfa multiple dose schedules comparison

Generation of randomisation sequence

The Clarke and Hughes trials did not provide a description regarding the generation of allocation; thus, they were classified as having an unclear risk of bias (Clarke 2007; Hughes 2013).

Allocation concealment

The Clarke and Hughes trials did not provide a description regarding the concealment of allocation; thus, they were judged to have an unclear risk of bias (Clarke 2007; Hughes 2013).

Blinding

The Hughes trial was classified as having a low risk of bias since there was blinding (Hughes 2013). The Clarke trial was also classified as having a low risk of bias, although this was an open-label trial, the outcome was objective (Clarke 2007).

Incomplete outcome data

The Clarke and Hughes trials reported less than 20% of withdrawals and dropouts, we therefore assessed this as having a low risk of bias (Clarke 2007; Hughes 2013).

Selective reporting

We judged both included trials to be free of selective reporting (Clarke 2007; Hughes 2013).

Other potential sources of bias

We did not identify any other potential sources of bias (Clarke 2007; Hughes 2013).

Effects of interventions

See: **Summary of findings for the main comparison**; **Summary of findings 2**; **Summary of findings 3**

We presented the data from agalsidase alfa and agalsidase beta separately because of differences in trial design and treatment doses.

Agalsidase alfa versus placebo

Two trials were included in this comparison with a total of 41 participants. 15 and 26 participants were enrolled in the trial conducted by Hughes and Schiffmann respectively (Hughes 2008; Schiffmann 2001).

Primary outcomes

1. Changes in globotriaosylceramide (Gb3) concentration in plasma and tissue

Two trials reported on this outcome at six months (end of treatment) (Hughes 2008; Schiffmann 2001). There was no statistically significant difference between treatment groups in the plasma Gb3 concentration, pooled MD -2.07 (95% CI -6.64 to 2.50) (with data entered from 39 of 41 participants) (Hughes 2008; Schiffmann 2001) (Analysis 1.1). There were no statistically significant differences between treatment groups regarding the subcategories: urine sediment Gb3, MD -812.00 (95% CI -1897.83 to 273.83); and kidney, MD -2.50 (95% CI -9.47 to -4.47) (Schiffmann 2001) (Analysis 1.2; Analysis 1.3). Hughes reported a statistically significant difference between the participants receiving agalsidase alfa and those receiving placebo for myocardial Gb3 levels at over three months and up to six months, MD 0.07 (95% CI -0.35 to 0.49) (Hughes 2008) (Analysis 1.4).

2. Death

Neither of the included trials reported on this outcome (Hughes 2008; Schiffmann 2001).

3. Pain (measured by the McGill Pain Questionnaire)

a. Acroparaesthesia

We intended to measure this outcome by the intensity and duration of acroparaesthesia as reported by the individual, however none of the included trials reported on this outcome (Hughes 2008; Schiffmann 2001).

b. Fabry crises

We planned to present the presence or absence of crises as a binary outcome, but none of the included trials reported on this outcome (Hughes 2008; Schiffmann 2001).

c. The Brief Pain Inventory severity

One trial reported on this outcome (Schiffmann 2001). There was a statistically significant difference favouring the participants receiving agalsidase alfa versus placebo in all the subcategories studied at over one month and up to three months, MD -2.10 (95% CI -3.79 to -0.41), at over three months and up to five months, MD -1.90 (95% CI -3.65 to -0.15), and at over five months and up to six months, MD -2.00 (95% CI -3.66 to -0.34) (Schiffmann 2001) (Analysis 1.5).

d. The Brief Pain Inventory pain-related quality of life

One trial reported on this outcome (Schiffmann 2001). There was no statistically significant difference between groups in the subcategories studied at over one month and up to three months, MD -0.90 (95% CI -2.73 to 0.93) and at over three months and up to five months, MD -1.80 (95% CI -3.77 to 0.17). However, at over five months and up to six months a significant difference favouring agalsidase alfa was noted, MD -2.10 (95% CI -3.92 to -0.28) (Schiffmann 2001) (Analysis 1.6).

Secondary outcomes

1. Effect of therapy on renal function

One trial reported on this outcome (Schiffmann 2001). Creatinine clearance and inulin clearance were used to estimate glomerular filtration rate. There were no statistically significant difference between both groups in the subcategories creatinine clearance at end of treatment (up to six months), and inulin clearance (up to six months) respectively, MD 10.30 (95% CI -15.37 to 35.97) and MD -0.50 (95% CI -21.36 to 20.36) (data entered for 24 of 26 participants) (Schiffmann 2001) (Analysis 1.7; Analysis 1.8).

There was no statistically significant difference between groups in the subcategories: glomeruli with mesangial widening at up to six months, MD -14.70 (95% CI -36.72 to 7.32); glomeruli with segmental sclerosis at up to six months and obsolescent glomeruli at up to six months; MD 3.80 (95% CI -2.35 to 9.95) and MD 6.50 (95% CI -8.93 to 21.93) (data entered for 21 out of 26 participants) (Schiffmann 2001) (Analysis 1.9; Analysis 1.10; Analysis 1.11).

2. Symptoms and complications of disease (such as renal failure, skin, cerebrovascular and cardiac complications)

Neither of the included trials reported on this outcome (Hughes 2008; Schiffmann 2001).

3. Parameters: echocardiographic

There was no statistically significant difference between groups for mean left ventricular wall thickness, MD -0.79 (95% CI -3.62 to

2.04); left ventricular internal diameter (diastolic), MD -3.70 (95% CI -11.73 to 4.33); left ventricular internal diameter (systolic), MD -2.70 (95%CI -9.91 to 4.51); and left ventricular ejection fraction, MD 1.88 (95%CI -4.68 to 8.44) (data entered for 14 out of 15 participants) (Hughes 2008) (Analysis 1.12).

4. Histologic analysis of microvascular capillary endothelial deposits of Gb3 in biopsy specimens

Neither of the included trials reported on this outcome (Hughes 2008; Schiffmann 2001).

5. Adverse effects of treatment

Neither of the included trials reported on this outcome (Hughes 2008; Schiffmann 2001).

6. Quality of life (as determined by the Short Form 36 (SF-36) and the impact of clinical variables on domain scores within the SF-36 (Smith 2000))

Neither of the included trials reported on this outcome (Hughes 2008; Schiffmann 2001).

Agalsidase beta versus placebo

Three trials were included in this comparison with a total of 146 participants. Banikazemi enrolled 82 participants, Bierer enrolled six participants and Eng enrolled 58 participants (Banikazemi 2007; Bierer 2006; Eng 2001).

Primary outcomes

1. Changes in globotriaosylceramide (Gb3) concentration in plasma and tissue

One of the included trials reported on this outcome in tissue (Eng 2001). There was a statistically significant difference favouring the participants receiving agalsidase beta versus placebo in three subcategories: kidney, MD -1.70 (95% CI -2.09 to -1.31); heart, MD -0.90 (95% CI -1.18 to -0.62); and composite, MD -4.80 (95% CI -5.45 to -4.15) (Eng 2001) (Analysis 2.1).

None of the included trials reported the effect on plasma concentrations (Banikazemi 2007; Bierer 2006; Eng 2001).

2. Death

There was no statistically significant difference in death as reported in one trial, RR 1.85 (95% CI 0.08 to 43.96) (Analysis 2.2). There was one death from a total of 51 participants in agalsidase beta and no deaths in the placebo group (n = 31) (Banikazemi 2007).

3. Pain (measured by the McGill Pain Questionnaire)

a. Acroparaesthesia

We intended to measure this outcome by the intensity and duration of acroparaesthesia as reported by the individual however none of the included trials reported this outcome (Banikazemi 2007; Bierer 2006; Eng 2001).

b. Fabry crises

We planned to present whether the participants had reported the presence or absence of crises as a binary outcome, but none of the included trials reported this outcome (Banikazemi 2007; Bierer 2006; Eng 2001).

Only one trial reported chest pain and fatigue; there was no statistically significant difference for any of these at 24 months; chest pain,RR 6.77 (95% CI 0.39 to 118.36) and fatigue, RR 6.77 (95% CI 0.39 to 118.36) (Banikazemi 2007) (Analysis 2.10; Analysis 2.12). Eng reported on pain related to Fabry disease at over three months and up to six months; there was no statistically significant difference with pain related to Fabry disease, RR 3.00 (95% CI 0.33 to 27.18) (Eng 2001) (Analysis 2.11).

Secondary outcomes

1. Effect of therapy on renal function

The number of renal events, defined by the authors as 33% increase in serum creatinine level; end-stage renal disease, were reported by Banikazemi. There was no statistically significant difference in the number of events between groups, RR 0.87 (95% CI 0.37 to 2.04) (Analysis 2.3) (Banikazemi 2007).

2. Symptoms and complications of disease (such as renal failure, skin, cerebrovascular and cardiac complications)

a. Cardiac events

Bierer reported cardiopulmonary exercise testing (Bierer 2006). There were no significant differences between groups in any of the sub-categories evaluated (average heart rate reserve, MD 21.30 (95% CI -1.28 to 43.88); average maximum oxygen uptake measured at peak exercise (in mL/(kg·min)), MD 0.22 (95% CI -0.94 to 1.38); maximum oxygen uptake measured at peak exercise, MD 2.60 (95% CI -13.16 to 18.36); and oxygen pulse average at peak exercise, MD 2.10 (95% CI -3.67 to 7.87)) (Analysis 2.4).

There were no significant differences in decrease in cardiopulmonary exercise test, RR 1.50 (95% CI 0.34 to 6.70) (Analysis 2.5) (Bierer 2006).

Banikazemi reported cardiac events and there was no significant differences between studied groups, RR 0.46 (95% CI 0.11 to 1.90) (Analysis 2.6) (Banikazemi 2007).

b. Cerebrovascular events

There was no significant difference in the number of cerebrovascular events between groups in the Banikazemi trial, RR 0.12 (95% CI 0.01 to 2.48) (Analysis 2.7). (Banikazemi 2007).

c. Percentage of participants achieving zero scores in microvascular endothelial deposits of globotriaosylceramide in the skin

For participants achieving zero scores in skin at five months, there was a statistically significant difference between groups in the Eng trial favouring the participants receiving agalsidase beta versus placebo in two subcategories: superficial endothelial cells, RR 19.67 (95% CI 4.13 to 93.63) and deep endothelial cells, RR 11.00 (95% CI 2.88 to 42.08) (Eng 2001). There was no significant difference between the analysed participants in each group in two further sub-categories: smooth muscle cells, RR 1.50 (95% CI 0.10 to 22.62), three and one participants contributed to this analysis in the agalsidase beta and placebo groups, respectively; or in perineurium cells, RR 1.04 (95% CI 0.07 to 15.72) (note not all the trial participants contribute to the analyses, please refer to the forest plot) (Analysis 2.8) (Eng 2001).

Eng reported data for participants achieving a zero score or a reduction in microvascular endothelial deposits of globotriaosylceramide in the skin (Analysis 2.9). There was

a statistically significant difference favouring the participants receiving agalsidase beta versus placebo in two sub-categories: superficial endothelial cells, RR 2.81 (95% CI 1.72 to 4.59); and deep endothelial cells, RR 2.79 (95% CI 1.67 to 4.67) (Eng 2001). There was no significant difference between groups in two further sub-categories: smooth muscle cells, RR 1.50 (95% CI 0.10 to 22.62) and in perineurium cells, RR 1.49 (95% CI 0.68 to 3.25). Three and one participants contributed to this analysis in the agalsidase beta and placebo groups, respectively.

3. Parameters echocardiographic

None of the included trials reported this outcome (Banikazemi 2007; Bierer 2006; Eng 2001).

4. Histologic analysis of microvascular capillary endothelial deposits of Gb3 in biopsy specimens

None of the included trials reported this outcome (Banikazemi 2007; Bierer 2006; Eng 2001).

5. Adverse effects of treatment

a. Any adverse event

Two trials reported adverse events; one at over three month and up to six months (Eng 2001) and one at 24 months (Banikazemi 2007).

There were statistically significant differences in favour of placebo regarding rigours at the following: over three and up to six months, RR 29.00 (95% CI 1.81 to 464.38) and, at 24 months, RR 10.94 (95% CI 1.54 to 77.95) (Analysis 2.13). Over three and up to six months there was no statistically significant difference comparing agalsidase beta to placebo, RR 7.00 (95% CI 0.92 to 53.36); however, at 24 months there was a statistically significant difference in favour of agalsidase beta compared to placebo in the reduction of fever, RR 8.51 (95% CI 1.18 to 61.58) (Analysis 2.14). One trial reported chills and there was no statistically significant difference at over three months and up to six months, RR 9.00 (95% CI 0.51 to 159.94) (Eng 2001) (Analysis 2.15). With regards to hypertension, there were no statistically significant differences between groups at both studied time points: over three and up to six months, RR 7.00 (95% CI 0.38 to 129.74); and at 24 months, RR 2.13 (95% CI 0.47 to 9.60) (Analysis 2.16).

Only one trial reported vomiting; there was no statistically significant difference at 24 months with vomiting, RR 8.00 (95% CI 0.47 to 137.27) (Banikazemi 2007) (Analysis 2.17). Eng reported on headache at over three months and up to six months; there was no statistically significant difference with headache, RR 2.50 (95% CI 0.53 to 11.86) (Eng 2001) (Analysis 2.18).

b. Any serious adverse events

None of the included trials reported this outcome (Banikazemi 2007; Bierer 2006; Eng 2001).

6. Quality of life (as determined by the Short Form 36 (SF-36) and the impact of clinical variables on domain scores within the SF-36 (Smith 2000))

None of the included trials reported this outcome (Banikazemi 2007; Bierer 2006; Eng 2001).

Agalsidase alfa versus agalsidase beta

Two trials were included in this comparison with a total of 103 participants (Sirrs 2014; Vedder 2007).

Primary outcomes

1. Changes in globotriaosylceramide (Gb3) concentration in plasma and tissue

The Vedder trial reported a median of 3.3 umol/l (range 1.45 to 6.42) and 3 umol/l (range 1.89 to 7.85) for 12 and 24 months of treatment, respectively in agalsidase alfa arm, while there was a median of 2.48 umol/l (range 1.40 to 3.93) and 2.23 umol/l (range 0.92 to 4.3) for 12 and 24 months of treatment, respectively in agalsidase beta arm (Vedder 2007).

Sirrs did not report on this outcome (Sirrs 2014).

2. Death

There was a death from multiple cerebral infarctions after 20 months in the agalsidase alfa treatment group, RR 3.00 (95% CI 0.13 to 69.09) (Vedder 2007) (Analysis 3.1). There was one death from a total of 18 participants in agalsidase alfa and no deaths in agalsidase beta (n = 18) (Vedder 2007).

3. Pain (measured by BPI-3)

a. Acroparaesthesia and Fabry crises

One trial described no significant reduction of pain score (BPI-3) after 12 months of treatment in either of the studied groups: alfa 0 (range 25 to 1); and beta 21.5 (range 24 to 3). The values did not change for analysis at the 24 month time point (Vedder 2007). The Sirrs trial did not evaluate pain (Sirrs 2014).

b. Fabry crises

We planned to present whether the participants had reported the presence or absence of crises as a binary outcome, but neither of the included trials reported this outcome (Sirrs 2014; Vedder 2007).

Secondary outcomes

1. Effect of therapy on renal function

The trial reported that renal insufficiency, defined as an increase of serum creatinine greater than 33%, progressed in two participants treated with agalsidase alfa, who had baseline GFR measurements of 22 and 30 ml/min (within 24 months). In the agalsidase alfa group, progression of renal insufficiency was seen in one other participant after 30 months of treatment (Vedder 2007).

2. Symptoms and complications of disease (such as renal failure, skin, cerebrovascular and cardiac complications)

a. Cardiac events

Two participants suffered from atrial fibrillation after 42 and 36 months of agalsidase beta treatment (Vedder 2007). Atrial fibrillation occurred in a male participant treated with agalsidase alfa for 30 months. There was no statistically significant difference for cardiac events, RR 0.47 (95% CI 0.05 to 4.60) (26 out of 29 participants analysed) (Vedder 2007) (Analysis 3.2).

b. Cerebrovascular events

One of the included trials did not report this outcome (Vedder 2007).

c. Percentage of participants achieving zero scores in skin

Neither of the included trials reported on this outcome (Sirrs 2014; Vedder 2007).

3. Echocradiographic Parameters

The Vedder trial reported LV Mass (g). There was a median of 244 g (range 157 to 424) and 294 g (range 196 to 502) for 12 and 24 months of treatment, respectively in the agalsidase alfa arm, while there was a median of 296 g (range 169 to 401) and 308 g (range 196 to 471) for 12 and 24 months of treatment, respectively in the agalsidase beta arm (Vedder 2007).

The Sirrs trial did not report on this outcome (Sirrs 2014).

4. Histologic analysis of microvascular capillary endothelial deposits of Gb3 in biopsy specimens

Neither of the included trials reported on this outcome (Vedder 2007; Sirrs 2014).

5. Adverse effects of treatment

a. Any adverse event

There was no significant difference in the number of any adverse events between groups in the Vedder trial, RR 0.36 (95% CI 0.08 to 1.59) (Vedder 2007) (Analysis 3.3).

The Sirrs trial did not report on this outcome (Sirrs 2014).

b. Any serious adverse events

There was no significant difference in the number of any serious adverse events between groups in the Vedder trial, RR 0.30 (95% CI 0.03 to 2.57) (Vedder 2007) (Analysis 3.4).

6. Quality of life (as determined by the Short Form 36 (SF-36) and the impact of clinical variables on domain scores within the SF-36 (Smith 2000))

One of the included trials did not report on this outcome, but it is included as an outcome in the protocol (Vedder 2007). We contacted the main author for further clarification and hope these data can be included in a future update of this review.

Sirrs did not report on this outcome (Sirrs 2014).

Multiple dose schedules of agalsidase alfa

Two trials were included in this comparison with a total of 36 participants (Clarke 2007; Hughes 2013).

Primary outcomes

1. Changes in globotriaosylceramide (Gb3) concentration in plasma and tissue

No significant difference was found among the treatment schedules for fasting plasma GB3 levels in the Hughes trial (Hughes 2013).

No statistically significant association between the magnitude of the reduction in plasma Gb3 and dose or dose frequency was described in the Clarke trial (Clarke 2007).

2. Death

Neither of the included trials reported on this outcome (Clarke 2007; Hughes 2013).

3. Pain (measured by BPI-3)

For the cross-over trial by Hughes (18 participants), there were no significant differences comparing 0.2 mg/ kg/ every two weeks versus 0.1 mg/ kg/ every week for mean pain score (Hughes 2013), MD -0.06 (95% CI -1.26 to 1.38), and for self assessed health state MD -1.20 (95% CI -14.10 to 11.70) (Hughes 2013) (Analysis 4.1; Analysis 4.2). There were no significant differences comparing 0.1 mg/kg/ every week versus 0.2 mg/kg/every week for mean pain score MD 0.06 (95% CI -1.25 to 1.37) and for self assessed health state, MD 0.30 (95% CI -12.70 to 13.30) (Hughes 2013) (Analysis 5.1; Analysis 5.2).

The Clarke trial did not report on this outcome (Clarke 2007).

Secondary outcomes

1. Effect of therapy on renal function

Neither of the included trials reported on this outcome (Clarke 2007; Hughes 2013).

2. Symptoms and complications of disease (such as renal failure, skin, cerebrovascular and cardiac complications)

Neither of the included trials reported on this outcome (Clarke 2007; Hughes 2013).

3. Echocardiographic Parameters

Neither of the included trials reported on this outcome (Clarke 2007; Hughes 2013).

4. Histologic analysis of microvascular capillary endothelial deposits of Gb3 in biopsy specimens

Neither of the included trials reported on this outcome (Clarke 2007; Hughes 2013).

5. Adverse effects of treatment

In the trial conducted by Clarke, the incidence of adverse events was not related to dose or dosing frequency (Clarke 2007).

The majority of moderate and severe AEs were reported by participants after treatment schedule A (0.2 mg/kg every other week) (Hughes 2013).

6. Quality of life (as determined by the Short Form 36 (SF-36) and the impact of clinical variables on domain scores within the SF-36 (Smith 2000))

Neither of the included trials reported on this outcome (Clarke 2007; Hughes 2013).

DISCUSSION

Summary of main results

This review included nine trials that were split between low and uncertain risk of bias and in addition statistical analysis was difficult due to the manner in which results were presented. Overall though, compared with participants receiving placebo, those treated with either agalsidase alfa or agalsidase beta experienced a reduction in Gb3 concentration in plasma and tissues. Although this finding is indicative of 'proof of concept', its clinical significance is uncertain as the trials examined did not provide specific information on correlation with clinical events or survival. In the agalsidase alfa comparison, even though we used a random-effects model (to better deal with heterogeneity), we found a high level of heterogeneity (I^2 = 91%) in the outcome plasma Gb_3 at up to six months. This method assumes that the effects being estimated in the different trials are not identical, but

follow some distribution. In this case the effect may have varied due to different population or intervention characteristics (such the dose, duration and regimen). Trial results indicate a significant effect of enzyme replacement therapy (ERT) on neuropathic pain, cardiac morphology and renal function, and a positive influence on pain-related quality of life. Treatment with ERT appears to be relatively well-tolerated. Infusion-related adverse events may be controlled by the use of pre-medication and the administration of the enzymes at a slower rate. Antibody formation has been reported in a significant proportion of treated individuals with trials indicating that the presence of neutralizing antibodies may potentially influence therapeutic outcome.

The effectiveness of therapy in delaying the onset or reducing the incidence and severity of Anderson-Fabry disease (AFD)-related complications, and its impact on long-term survival remains unclear though clearly it does have a positive effect on some aspects of the disease. Heterogeneity in clinical phenotype means long-term, large cohort studies are required. This is being addressed primarily through patient registries. It will also be important to look in detail at effectiveness and safety of ERT according to patient sub-populations, such as gender, later-onset versus classic phenotypes, type of mutation, age and presence of chronic injury at initiation of treatment.

The low number of eligible trials for this Cochrane analysis together with the low number of participants included in the trials, due to the rare nature of AFD, prevented us performing these sub-analyses. It is likely that advanced disease prior to the start of treatment influences outcome and that the earlier the initiation of treatment the greater the effect on preventing complications. Trials in asymptomatic or minimally affected individuals may provide information on the effectiveness of therapy in preventing or delaying the onset of symptoms or disease-related complications (Ramaswami 2007; Ries 2006; Ries 2007; Wraith 2008).

Overall completeness and applicability of evidence

A limitation is the fact that pain often does not feature in the trials. It is known that most cases of pain resolve spontaneously, even in the absence of any treatment, and pain is a subjective outcome and thus depends on the self-reports provided by the participants, so it is difficult to provide objective evidence. Only Schiffmann reported the Brief Pain Inventory comparing agalsidase alfa versus placebo (Schiffmann 2001). No included trial (Banikazemi 2007; Bierer 2006; Eng 2001) comparing agalsidase beta versus placebo reported on pain and, only Hughes 2013 reported on it comparing 0.2 mg/kg/every 2 weeks versus 0.1 mg/kg/every week and, 0.1 mg/kg/every week versus 0.2 mg/kg/every week.

Quality of the evidence

The methodological quality of the included trials was generally unclear for the random sequence generation and allocation concealment (Bierer 2006; Clarke 2007; Eng 2001; Hughes 2008; Hughes 2013; Sirrs 2014). Some methodological aspects of one trial (with inadequate blinding of outcome assessment, participants and caregivers, as well as incomplete outcome data and selective reporting outcome) resulted in this trial having a high risk of bias (Vedder 2007).

Potential biases in the review process

Despite our thorough search in various databases we might have overlooked trials, especially with regard to the grey literature. However, we contacted the authors of the included trials to ask whether they had undertaken any other relevant trials comparing ERT to other interventions, placebo or no interventions, for treating AFD.

Agreements and disagreements with other studies or reviews

The results of this review reflect those of previous versions of the review (El Dib 2010; El Dib 2013). A recent systematic review undertaken to analyse the currently available data concerning quality of life (QoL) measurement, concluded no definite conclusions could be drawn from the trials on the effect of ERT on QoL (Arends 2015). A review of the literature comparing two different products the Replagal™) (agalsidase alfa) and Fabrazyme® (agalsidase beta) formed the same conclusion as this review in that there is little evidence for choosing one over the other (Riccio 2013).

There are some clinical single entity studies demonstrating beneficial effect of ERT. The effect of agalsidase beta 1 mg/kg bi-weekly was assessed in a phase 4 placebo-controlled study of both untreated and treated individuals with Fabry disease with mild-to-moderate renal involvement (i.e., serum creatinine measurements of ≥1.2 mg/dl and < 3.0 mg/dl) on progressive white matter lesions and stroke. The authors concluded that "ERT may reduce the progression of vascular disease, even in advanced FD patients, suggesting that early treatment may stabilize WML progression and stroke risk" (Fellgiebel 2014). A cohort study evaluated the progression of left ventricular hypertrophy in untreated men with Fabry disease and assessed the effects of agalsidase beta on left ventricular hypertrophy (Germain 2013). The authors analysed 115 men treated with agalsidase beta (1 mg/kg/2 weeks) and 48 untreated men. The authors found for men in whom treatment was initiated at the age of 18 years to under 30 years, mean left ventricular mass slope was -3.6 g/year (n = 31) compared with + 9.5g/year in untreated men of that age (n = 15). The authors also found that untreated men had a higher risk of having faster increases in left ventricular mass compared with treated men (Germain 2013).

Schiffmann conducted an open-label study with 11 children who completed 26-weeks of intravenous 0.2 mg/kg agalsidase alfa (Schiffmann 2014). The authors found all participants experienced at least one adverse event, but no death occurred and cardiac outcomes remained stable. Tøndel evaluated five years of treatment with agalsidase alfa or agalsidase beta in 12 people aged seven to 33 years (Tøndel 2013). Biopsy findings from all participants showed total clearance of glomerular endothelial and mesangial cell inclusions after a median of follow up of 65 months. Another study assessed 105 adults with Fabry disease who had received agalsidase beta (1.0 mg/kg body weight) for more than a year and, the authors found that "patients receiving regular agalsidase beta dose had a stable disease course, but dose reduction led to worsening of renal function and symptoms" (Weidemann 2014).

A randomized controlled trial that evaluated pharmacokinetic parameters of a recombinant agalsidase beta (Agal) ERT in 18 healthy adult volunteers found no immunogenicity or any

significant infusion-related reactions; although overall there were seven adverse events that were resolved without any complications (Kim 2014).

Rombach study evaluated 59 people with Fabry disease treated with either agalsidase alfa or beta for at least one year (Rombach 2012). They found 17 out of 59 individuals developed anti-agalsidase antibodies during the first year of treatment and, the authors concluded that the presence of these antibodies is associated with a less robust decrease in plasma lysoGb3 as well as a negative urinary Gb3 reduction.

AUTHORS' CONCLUSIONS

Implications for practice

Trials comparing ERT to placebo show significant results in regard to microvascular endothelial deposits of globotriaosylceramide and in pain-related quality of life. There is, however, no evidence identifying if the alfa or beta form is superior or the optimal dose or frequency of ERT. It is always difficult to study rare diseases, given the limited population available to study and given that many of these disorders, such a AFD, are long-term, chronic illnesses and a long follow up is required. With regards to safety, adverse events (i.e. rigors, fever) were more significant with agalsidase beta as compared to placebo. The long-term influence of enzyme replacement therapy on risk of morbidity and mortality related to AFD remains to be established. There is also a need to understand prognostic determinants and therapeutic outcome, which may allow stratification of patients and identification of the subset of patients most likely to achieve the best results with treatment.

Implications for research

This review highlights the need for continued research into the use of ERT for AFD. Subsequent trials should help define the use of ERT and other therapeutic options, e.g. substrate reduction therapy and pharmacological chaperones, as these become available and should be considered either in combination or as monotherapy in the management of people with AFD.

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* Indicates the major publication for the study

CHARACTERISTICS OF STUDIES

Characteristics of included studies *[ordered by study ID]*

Banikazemi 2007

Methods	Trial design: parallel design double-blind RCT. Multicenter Setting: 41 referral centers (university or research hospitals) in nine countries in North America and Europe. Period: February 2001 to January 2004. Sample size calculation: reported (80 participants to provide 80% power for detecting a treatment effect on the basis of log rank testing by using a 10% dropout rate; a 14-month enrolment period and 18 months of follow up; type I error of 0.05 (2-sided); and expected events rates over 2 years of 40% and 10% for participants in the placebo and agalsidase beta groups, respectively, as predicted by an estimated 20% to 30% decline per year in estimated).
Participants	Of the 252 patients screened, 82 eligible patients (ITT population) were treated at 26 sites in 6 countries. Mean age: agalsidase beta group 46.9 years and, placebo group 44.3 years. Sex: agalsidase beta group 88% men and 12% women and, placebo group 87% man and 13 % women. Inclusion criteria: participants were at least 16 years of age with clinical evidence of AFD. Exclusion criteria: participants who were undergoing dialysis or were schedule for kidney transplantation; those with documented transient ischemic attacks, ischemic stroke, unstable angina, or myocardial infarction with 3 months of trial entry; and those with confounding conditions or other clinically significant comorbid conditions.
Interventions	IV infusion of agalsidase beta (mg/kg of body weight) (n = 51) or placebo every two weeks (n = 31). Follow up: 18 months.
Outcomes	Primary end point: the time to first clinical event (renal, cardiac, or cerebrovascular event or death).

Banikazemi 2007 *(Continued)*

	A renal event was defined as a 33% increase in serum creatinine level from baseline (2 consecutive values) or end-stage kidney disease requiring long-term dialysis or transplantation. A cardiac event was defined as myocardial infarction; new symptomatic arrhythmia requiring antiarrhythmic medication, pacemaker, direct current cardioversion, or defibrillator implantation; unstable angina defined by national practice guidelines and accompanied by electrocardiographic changes resulting in hospitalization; or worsening congestive heart failure requiring hospitalization. A cerebrovascular event was defined as a stroke or transient ischemic attack documented by a physician. participants were allowed to transition to open-label agalsidase beta after an independent adjudication board confirmed that a primary end point event had occurred. The following measures were also performed at baseline and at the final trial visit or time of trial withdrawal: serum creatinine level; proteinuria; ratio of urinary albumin to urinary creatinine; 12-lead electrocardiography; echocardiography; neurologic examination; head magnetic resonance imaging; Brief Pain Inventory; exercise tolerance; plasma globotriaosylceramide level; Fabry symptom assessment; physical examination; blood chemistries; urinalysis; IgG antibody titers to agalsidase beta; and optional skin biopsy. Safety monitoring included physician evaluation and documentation of adverse events.
Notes	The Genzyme Corporation and the National Center for Research Resources supported the trial. We contacted the author on 09 October 2015 for further information and, we are awaiting their reply.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Randomization codes were computer-generated.
Allocation concealment (selection bias)	Low risk	Randomization codes were maintained centrally at a secure location. The 2:1 randomization scheme was blocked (block size of 3, which was not revealed to investigators) at each site.
Blinding (performance bias and detection bias) All outcomes	Low risk	Trial materials were packaged identically, and sponsor staff, investigators, and patients were blinded to treatment allocation.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Withdrawals and drop outs, were noted by Banikazemi to be less than 20%. ITT was used for the primary outcome only.
Selective reporting (reporting bias)	Low risk	No evidence.
Other bias	High risk	The Genzyme Corporation and the National Center for Research Resources supported the trial.

Bierer 2006

Methods	Trial design: parallel design RCT. Single-center or multicenter: not reported. Setting: not reported. Period: 10 weeks.

Bierer 2006 *(Continued)*

	Sample size calculation: not reported.
Participants	15 individuals with AFD, but only 6 participants were randomized (4 treatment; 2 placebo). Sex: 5 male, and 1 female. Mean age: male was 35 years and female was 42 years.
Interventions	Placebo (saline) or enzyme replacement therapy (agalsidase beta 1 mg/kg every other week - Fabrazyme®). Follow up: 18 months.
Outcomes	Cardiopulmonar exercise test, forced expiratory volume and forced vital capacity. History and physical examination, a baseline electrocardiogram, transthoracic echocardiogram, and a pulmonary function test (spirometry) were also performed.
Notes	First, the authors compared baseline cardiopulmonary exercise tests performed noninvasively, next, they assessed the impact of alfa galactosidase A on exercise tolerance by serial non-invasive cardiopulmonary exercise tests. The 6 participants randomized were part of a phase IV trial evaluating enzyme replacement therapy. Nine additional participants completed invasive cardiopulmonary exercise tests at baseline examinations. These participants did not have follow-up exercise tests and were not randomized to drug or placebo, neither evaluated in this systematic review. The funding was provided by Genzyme Corporation. We contacted the author on 09 October 2015 for further information and, we are awaiting their reply.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Stated as "randomized".
Allocation concealment (selection bias)	Unclear risk	Not reported.
Blinding (performance bias and detection bias) All outcomes	Unclear risk	Stated as "randomized in a double-blind fashion".
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Not reported.
Selective reporting (reporting bias)	Low risk	Not reported.
Other bias	High risk	The funding was provided by Genzyme Corporation.

Clarke 2007

Methods	Trial design: parallel design open label, RCT. Multicenter.

Clarke 2007 *(Continued)*

	Setting: participating study sites included the National Institutes of Health, Bethesda, MD (four patients); Hospital for Sick Children, Toronto, ON, Canada (seven participants); Dalhousie University, Halifax, NS, Canada (3 participants), and the Charles University, Prague, Czech Republic (4 participants). Period: 10 weeks' duration. Sample size calculation: not reported.
Participants	N: 18 Sex: male only Mean age: overall not reported. Inclusion criteria: ERT-naive males (18 years or older) with a confirmed diagnosis of Fabry disease were eligible for inclusion in the study. AFD could be confirmed by mutation analysis or by a demonstration of a deficiency of-Gal A activity (4.0 nmol/mL per hour in plasma or serum or 8% of the average mean normal in leukocytes). In addition, participants must have had at least one sign or symptom of AFD, including neuropathic pain, angiokeratoma, corneal verticillata, cardiomyopathy, hypo- or anhydrosis, abdominal pain and/or diarrhoea, serum creatinine 1.0 mg/dL, and proteinuria 300 mg/24 hr. Exclusion criteria: being on kidney dialysis or having received a kidney transplant.
Interventions	Participants were randomly assigned to one of five dosing groups stratified by baseline plasma Gb3 levels (low, 4 to11.5 nmol/mL; high,11.5 nmol/mL). The agalsidade alfa treatment groups were: (1) 0.1 mg/kg weekly (n = 4); (2) 0.2 mg/kg every other week (n = 4); (the standard dose); (3) 0.2 mg/kg weekly (n = 4); (4) 0.4 mg/kg every other week (n = 3); (5) 0.4 mg/kg weekly (n = 3). All doses were infused intravenously at a rate of 0.1 mg/kg per 20 minutes.
Outcomes	To investigate the pharmacokinetics and pharmacodynamics of various dosing regimens of agalsidase alfa. The primary efficacy endpoint variable was change in plasma Gb3 level from baseline to the day of the final infusion.
Notes	We contacted the author on 09 October 2015 for further information and, we are awaiting their reply.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	"Patients were randomly assigned to one of five dosing groups stratified by baseline plasma Gb3 levels (low, 4 to 11.5 nmol/mL; high,11.5 nmol/mL)". No direct statement of how the sequence is generated.
Allocation concealment (selection bias)	Unclear risk	"Patients were randomly assigned to one of five dosing groups stratified by baseline plasma Gb3 levels (low, 4 to11.5 nmol/mL; high,11.5 nmol/mL". No direct statement of how the generated sequence is concealed.
Blinding (performance bias and detection bias)	Low risk	Although the authors referred this was an open label study, the outcome is objective, and then it leads to lower probability to detection bias.

Clarke 2007 *(Continued)*

All outcomes		
Incomplete outcome data (attrition bias) All outcomes	Low risk	All participants completed the 10-week study.
Selective reporting (reporting bias)	Low risk	No evidence.
Other bias	Low risk	No evidence.

Eng 2001

Methods	Trial design: parallel design phase-3 double-blind RCT. Multicenter Setting: not reported. Period: not reported. Sample size calculation: not reported.
Participants	58 participants with AFD (56 males) (29 each group). Age average in the placebo group 28.4 years and in the treated group 32.0 years. Inclusion criteria: patients should be over 16 years old, with alfa-galactosidases levels in the plasma lesser than 1.5 nmol/hour/mL or levels of leucocytes activity smaller than 4 nmol/hour/mg and, levels of creatine lesser than or equal to 2.2 mg/dL. Exclusion criteria: participants who had carried through renal transplant or were carrying through dialysis.
Interventions	Participants received placebo or agalsidase beta 1 mg/kg intravenously every 2 weeks. Follow up: 5 months.
Outcomes	Primay endpoint was percentage of patients in whom renal microvascular endothelial deposits of Gb_3 were cleared. It was also evaluated the histologic clearance of microvascular endothelial deposits of Gb_3 in the endomyocardium and skin, changes in the level of pain and the quality of life, urinary creatine, urinary proteic excretion, renal function and dermatological characteristics of glicolipides accumulation in the dermis. The individual scores for the kidney-, heart-, and skin-biopsy specimens and the composite scores for all 3 types of specimens were compared at baseline and after the week-20 infusion.
Notes	Authors of the trial belonged to Genzyme Corporation, Cambridge, Massachusetts, USA. We contacted the author on 09 October 2015 for further information and, we are awaiting their reply.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Stated as "randomized".

Eng 2001 *(Continued)*

Allocation concealment (selection bias)	Unclear risk	Not reported.
Blinding (performance bias and detection bias) All outcomes	Unclear risk	Stated as "double-blind". Information given on two outcomes: each renal biopsy was reviewed under light microscopy by three independent renal pathologists who were blinded to treatment status of the patient at the time of biopsy; immunofluorescence trials were scored blinded.
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Not reported.
Selective reporting (reporting bias)	Low risk	No evidence.
Other bias	High risk	Authors of the trial belonged to Genzyme Corporation, Cambridge, Massachusetts, USA. We contacted the author on 09 October 2015 for further information and, we are awaiting their reply.

Hughes 2008

Methods	Trial design: parallel design double-blind RCT. Single-center or multicenter: not reported. Setting: not reported. Period: not reported. Sample size calculation: not reported.
Participants	15 male with AFD. Age: average of 37 years.
Interventions	The participants received placebo (N = 8) or enzyme replacement therapy with alfa agalsidase 0.2 mg/kg every 40 minutes, twice a week (n = 7) and, an additional of more 36 months. Follow up: 6 months.
Outcomes	The primary efficacy endpoint was myocardial Gb_3 content; the secondary efficacy endpoint was reduction of the left ventricular mass by MRI assessment. In addition, QRS duration and levels of Gb_3 in cardiac tissue, urine sediment and plasma, echocardiography, electrocardiography, pure-tone audiometry, impedance audiometry and otoacoustic emission testing were also performed. Adverse events were computed.
Notes	No conflict of interest reported by the trial investigators. We contacted the author on 09 October 2015 for further information and, we are awaiting their reply.

Risk of bias

Bias	Authors' judgement	Support for judgement

Hughes 2008 *(Continued)*

Random sequence generation (selection bias)	Unclear risk	Not reported.
Allocation concealment (selection bias)	Unclear risk	Not reported.
Blinding (performance bias and detection bias) All outcomes	Low risk	Stated as double blind. All data were independently analysed by Royal Free Hospital investigators. The data remained blinded until the database was unlocked and the statistical analyses performed.
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Not reported.
Selective reporting (reporting bias)	Low risk	No evidence.
Other bias	High risk	Trial authors received travel and research funding and honoraria for speaking and advisory boards from Shire HGT, Genzyme and Amicus.

Hughes 2013

Methods	Trial design: cross-over double-blinded placebo RCT. Single-center or multicenter: multicenter. Setting: 2 hospitals (Royal Free Hospital, London and Addenbrookes Hospital, Cambridge). Period: 4 weeks. Sample size calculation: not reported.
Participants	N = 18 (cross-over). Study participants with AFD (confirmed α-galactosidase A deficiency and mutation of the α-galactosidase A gene), were at least 18 years of age, and had been treated with agalsidase alfa (0.2 mg/kg IV every second week) for a minimum of three months to minimise the possibility that differences seen between the schedules were related to ongoing positive trajectory of response at the beginning of therapy.
Interventions	1) Schedule A (the currently approved treatment): 0.2 mg/kg agalsidase alfa administered every other week as a 40 minute IV infusion. To maintain consistency of weekly infusions in each schedule and therefore the blind, placebo was administered in the alternate week to agalsidase alfa in schedule A. 2) Schedule B: 0.1 mg/kg agalsidase alfa administered once a week as a 40 minute IV infusion. 3) Schedule C: 0.2 mg/kg agalsidase alfa administered once a week as a 40 minute IV infusion.
Outcomes	The primary outcome variable was self-assessed health state, measured by the visual analogue scale ('thermometer') item of the European quality of life questionnaire (the EQ-5D: Euroqol Group 1990). Secondary outcome variables was pain, assessed as the average composite pain severity dimension of the brief pain inventory (BPI) short form. Safety assessments included physical examination, 12-lead electrocardiogram (ECG), clinical laboratory testing, and vital sign measurements and, adverse events (AEs).
Notes	We contacted the author on 09 October 2015 for further information. The authors replied to our comments on 24 October 2015 saying that they have contacted the sponsor of the original study in regard to the randomisation, but no further information was provided.

Hughes 2013 *(Continued)*

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not reported.
Allocation concealment (selection bias)	Unclear risk	Not reported.
Blinding (performance bias and detection bias) All outcomes	Low risk	All participants received weekly infusions, which ensured that the blinding was upheld and during the schedule of infusions every second week.
Incomplete outcome data (attrition bias) All outcomes	Low risk	20 participants entered the study, 19 received at least one dose of study medication and therefore constitute the safety population. One participant was screened but did not proceed to study medication due to travel difficulties. 18 completed all three dosing schedules and constitute the ITT population.
Selective reporting (reporting bias)	Low risk	No evidence.
Other bias	Low risk	No evidence.

Schiffmann 2001

Methods	Trial design: parallel design double-blinded placebo RCT. Single-center or multicenter: not reported. Setting: the Clinical Research Center of the National Institutes of Health. Period: 6 months. Sample size calculation: not reported.
Participants	26 males with AFD. Age ranged between 16 and 56 years.
Interventions	Placebo (n = 12 and 11 randomized and completed trial, respectively) or alfa galactosidase A (n = 14 randomized and completed trial) , twice a week managed intravenously. Follow up: not reported.
Outcomes	Transversal doppler, left ventricular volume, heart rate, stroke volume, cerebral blood flow. The following Doppler parameters were obtained: peak flow velocity, mean flow velocity, end-diastolic velocity, pulsatility index, and resistance index. Neuropathic pain measured by the Brief Pain Inventory, renal function, cardiac function, storage material, quantitative sensory testing, skin biopsy, and Gb_3 analyses.
Notes	No conflict of interest reported by the trial investigators. We contacted the author on 09 October 2015. The author replied to our comments at the same day.

Schiffmann 2001 *(Continued)*

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Random tables (information retrieved by contact with the author).
Allocation concealment (selection bias)	Low risk	Randomization schedule was prepared prior to the start of the trial and was provided to an unblinded pharmacist in the research pharmacy at the National Institutes of Health. No other medical or sponsor personnel had access to the randomization code until the trial was completed. The randomization was generated by the biotechnology company (the latter information was retrieved by contact with the author).
Blinding (performance bias and detection bias) All outcomes	Unclear risk	There was no detail whether clinicians, patients, outcome assessors were blinded to the treatment groups.
Incomplete outcome data (attrition bias) All outcomes	Low risk	1 participant, randomized to the placebo trial arm, withdrew from the trial for personal reasons and 3 further participants (1 from the ERT group and 2 from the placebo group) declined the follow-up acetazolamide challenge arm of the trial at completion of the trial. A further patient had suffered a lacunar infarct 10 years prior to commencement of the present trial.
Selective reporting (reporting bias)	Low risk	No evidence.
Other bias	Low risk	No conflict of interest reported by the trial investigators.

Sirrs 2014

Methods	Trial design: parallel design RCT. Multicenter study (5 centers). Setting: Canada. Period: Median follow up was 23.0 ±8.1 months. Sample size calculation: There was a sample size calculation done before the start of the study (information retrieved by contact with the author).
Participants	N: 67 randomized participants. Age: mean of 47.6 years Sex: 55 females; 37 males Inclusion criteria: the CFDI is a nationwide study of all patients in Canada with AFD between ages 5 and 85. All Canadian citizens with AFD are eligible for inclusion.
Interventions	Participants newly meeting criteria for ERT and randomized 1:1 to agalsidase beta 1.0 mg/kg q2wks (n = 30) or agalsidase alfa 0.2 mg/kg q2wks (n = 62) (Cohort 1b). Follow up: 6 months.

Sirrs 2014 *(Continued)*

Outcomes	Compare the effects of agalsidase alfa and agalsidase beta on a composite clinical outcome consisting of renal (dialysis, transplant, or reduction in GFR by 50%), cardiac (admission for cardiac event), neurologic (stroke or sudden unilateral hearing loss) or death.
Notes	Cohort 1a - participants on ERT when the CFDI began who maintained their baseline treatment assignment (not randomised and therefore not included in the review). No data are available for only the original 1b cohort and, therefore no data can be used in analysis. We contacted the author on 08 October 2015 for further information. The author replied to our comments at the same day.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Randomization was done manually in blocks of 4 (information retrieved by contact with the author).
Allocation concealment (selection bias)	Low risk	Randomization was done by a third party [information retrieved by contact with the author].
Blinding (performance bias and detection bias) All outcomes	Low risk	Although the authors stated that "the sites and the patients are informed of the drug choice after randomization so the treatment assignment is not blinded" [information retrieved by contact with the author], we considered it as low risk of bias as the composite clinical outcome is objective and less likely to be affected by unmasking.
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Not reported.
Selective reporting (reporting bias)	Low risk	No evidence.
Other bias	Low risk	No evidence.

Vedder 2007

Methods	Trial design: parallel design open-label RCT. Multicenter. Setting: two centers in Norway (the Academic Medical Center and the Center for Medical Genetics and Molecular Medicine, Haukeland University Hospital). Period: May 2002 and December 2004. Sample size calculation: reported (90% and an alpha of 5% (one-sided), it was predicted that at least 18 patients (9 in each group) with an increased LVmass were required, i.e. a 10% larger reduction in LVmass by agalsidase alfa treatment than agalsidase beta treatment).
Participants	36 randomized participants (18 males and 18 females). Age range: 19 and 76 years.

Vedder 2007 *(Continued)*

Interventions	Agalsidase alfa (n = 20 and 18 randomized and analysed, respectively) or agalsidase beta (n = 16 randomized and analysed) at equal dose of 0.2 mg/kg biweekly for at least 12 months.

Outcomes	Primary endpoint:
	• Reduction of left ventricular mass on echocardiography
	Secondary endpoints:
	• Improvement of renal function as measured by GFR.
	• Reduction of glycolipid accumulation in skin tissue (LM and biochemistry).
	• Reduction in pain as measured by the BPI.
	• Reduction in glycosphingolipid in plasma and 24-hour urine.
	Tertiary endpoint:
	• Quality of life scores (SF-36).
	• Treatment failure defined as:
	  • progression of renal disease (33% increase in serum creatinine, need for dialysis or transplantation);
	  • progression of cardiac disease (new infarction, need for cardioversion, or anti-arrhythmic drugs, heart-failure necessitating hospitalizations;
	  • occurrence of a new CVA as diagnosed by a neurologist or new lacunar infarctions on MRI as assessed by an experienced neuroradiologist.

Notes	We contacted the author on 09 October 2015 for further information and, we are awaiting their reply. International Standard Randomized Clinical Trial: ISRCTN45178534

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Permuted block randomisation, with a block size of 4 participants. Manual randomization, envelopes generated by people not involved in obtaining informed consent.
Allocation concealment (selection bias)	Low risk	Envelopes checked by two persons not involved in obtaining informed consent.
Blinding (performance bias and detection bias) All outcomes	High risk	The authors reported that the envelopes were opened by the investigator in the presence of the patient.
Incomplete outcome data (attrition bias) All outcomes	High risk	In the LVMass analysis there were withdrawal rates of 50% and 62.5% in the agalsidase alfa and beta groups, respectively.
Selective reporting (reporting bias)	High risk	Quality of life is included as an outcome in the protocol, but not stated in the paper. However, we contacted the author to know if they have assessed this outcome. The author replied and said that they evaluated the QoL using SF36 questionnaires, but for the analysis presented in the paper, they did not use these data. They are willing to send us the data and we will include these in a future update.
Other bias	Low risk	No conflict of interest was reported by the trial investigators.

AEs: adverse events

AFD: Anderson-Fabry disease
BPI: Brief Pain Inventory
CFDI: Canadian Fabry Disease Initiative
CVA: cerebral vascular accident
ECG: electrocardiogram
ELISA: enzyme-linked immunosorbent assay
GRF: glomerular filtration rate
ITT: intention-to-treat
IV: intravenous
MRI: magnetic resonance imaging
QoL: quality of life
RCT: randomized controlled trial

Characteristics of excluded studies *[ordered by study ID]*

Study	Reason for exclusion
Alamartine 2005	Case series.
Banikasemi 2005	Case series.
Beck 2004	Cohort study.
Beer 2006	Case series.
Breunig 2006	Case series.
Cartwright 2004	Case series.
Elliott 2006	Cohort study.
Eto 2005	Case series (all participants received 1 mg/kg of agalsidase beta, no comparator treatment). The authors reported the results of an open-label phase-2 study that was undertaken to evaluate whether ethnic differences exist that would affect agalsidase beta treatment of people with AFD.
Fellgiebel 2014	Phase 4 agalsidase beta placebo-controlled analysis of untreated and treated AFD patients with mild-to-moderate renal involvement.
Fernhoff 2011	Case series.
Germain 2007	Case series (58 people who had classic AFD and completed a 20-week, double-blind, randomized, placebo-controlled, phase-3 study of agalsidase were transitioned to an open-label extension trial to receive bi-weekly 1 mg/kg agalsidase for up to an additional 54 months, no placebo).
Germain 2013	Cohort study.
Guffon 2002	Case series.
Guffon 2004	Case-control study.
Hajioff 2006	Case series.
Hilz 2004	Cohort study.
Jardim 2006	Case series.
Jardim 2006b	Case series.

Study	Reason for exclusion
Kalliokoshi 2006	Case series.
Kampmann 2002	Controlled trial with a cross-over to open label.
Kim 2014	RCT, but evaluated only pharmacokinetic parameters and safety.
Kobayashi 2005	Case series.
Kosch 2004	Case series.
Linthorst 2004	Case series.
Linthorst 2006	Case series.
Mignani 2004	Case series.
Mills 2004	Case series.
Pisani 2005	Case series.
Ramaswami 2007	Case series.
Ries 2006	Case series.
Rombach 2012	Case series.
Schiffmann 2003	Case series.
Schiffmann 2006	Case series (participants who had completed a 6-month randomized placebo-controlled trial enrolled in an open-label extension study. All the participants received agalsidase alfa 0.2 mg/kg).
Schiffmann 2013	Case series.
Schiffmann 2014	6-week, open-label, every-other-week, IV 0.2 mg/kg agalsidase alfa. The study was divided into two phases (before and after an agalsidase alfa manufacturing process change).
Sirrs 2011	Cohort study.
Spinelli 2004	Case series.
Tsuboi 2014	Non-randomised trial.
Tøndel 2013	Case series.
Utsumi 2005	Case series.
Weidemann 2003	Case series.
Weidemann 2014	Observational study.
West 2011	Cohort study.

IV: intravenous

Characteristics of studies awaiting assessment *[ordered by study ID]*

Benjamin 2014

Methods	Randomized controlled trial.
Participants	People with AFD. As of 15 December 2011, 60 males and 120 females have been screened. The mean (SD) age was 41 (14) years. 154/180 participants carried a missense mutation. 136/154 (88 %) participants carried an addressable mutation. For 18/154 (12%), the mutation was not considered addressable. 68 unique missense mutations were confirmed. Of these, 56 (82%) were considered addressable. 15 mutations were not previously described. Frequent substitutions were N215S (17 participants), R342Q (8 participants), R112H (7 participants), and R301Q (7 participants). All four were addressable. In summary, a majority of those with AFD screened for FACETS carried addressable missense mutations and were potentially eligible for the study. Screening for FACETS is complete and 67 participants have been randomized.
Interventions	Migalastat HCl (AT-1001, GR181413A), an investigational pharmacological chaperone was studied in Phase 3 for AFD (FACETS study) (AT1001-011).
Outcomes	Plasma lyso-Gb3 levels.
Notes	FACETS study (NCT00925301). Conflict of Interest declared.

Hughes 2014

Methods	Migalastat - new Intervention (investigational) that is seeking marketing approval mid-2015 for people with AFD with amenable mutations.
Participants	The Phase 1, randomized single IV dose study is evaluating the safety and tolerability in a 2-way cross-over arm, the absolute bioavailability of migalastat in healthy volunteers (Study 018). This study will identify the optimal dose of migalastat for use in ATB100C, and will inform the design of Study 019 in people with AFD.
Interventions	A next-generation AFD ERT based on CHARTTM, in which the migalastat chaperone binds and stabilizes alpha-Gal A in its properly folded and active form (denoted ATB100C), may result in increased uptake of active enzyme into target tissues and improved tolerability. A Phase 1 pharmacokinetics study of IV migalastat (Study 018), will be followed by a Phase 1/2 study to evaluate the activity, safety, and pharmacokinetics of ATB100C (Study 019). Study 018 will characterize the pharmacokinetics of IV migalastat, and inform dosing for further study with ATB100C. Study 019 is designed to provide proof-of-concept for this next-generation ERT in AFD.
Outcomes	Key measurements in Study 019 will include plasma lyso-GB3, antibodies, plasma α-Gal A activity, and pharmacokinetics of migalastat and ATB100C.
Notes	Conflict of Interest declared.

Wijburg 2015

Methods	Randomized, open-label, parallel-group, phase 3B clinical trial.
Participants	Males aged 5 - 18 years with complete α-galactosidase A deficiency, without symptoms of major organ damage.
Interventions	2 doses of agalsidase beta compared.

Wijburg 2015 *(Continued)*

Outcomes	Plasma and urinary GL-3 levels, plasma lyso-GL-3, GL-3 accumulation, mean GFR, median urinary albumin/creatinine ratio.
Notes	

ERT: enzyme replacement therapy
AFD: Anderson-Fabry disease
GFR: glomerular filtration rate
IV: intravenous

DATA AND ANALYSES

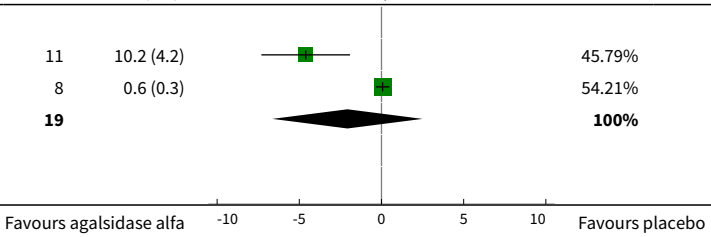
Comparison 1. Agalsidase alfa vs placebo

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Plasma Gb3	2		Mean Difference (IV, Random, 95% CI)	Subtotals only
1.1 At up to 6 months	2	39	Mean Difference (IV, Random, 95% CI)	-2.07 [-6.64, 2.50]
2 Urine sediment Gb3	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
2.1 At up to 6 months	1		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
3 Kidney Gb3	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
3.1 At up to 6 months	1		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
4 Myocardial globotriaosylceramide levels	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
4.1 Over 3 months and up to 6 months	1		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
5 The Brief Pain Inventory Severity	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
5.1 Over 1 month and up to 3 months	1		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
5.2 Over 3 months and up to 5 months	1		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
5.3 Over 5 months and up to 6 months	1		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
6 The Brief Pain Inventory pain-related QoL	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
6.1 Over 1 month and up to 3 months	1		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
6.2 Over 3 months and up to 5 months	1		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
6.3 Over 5 months and up to 6 months	1		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
7 Creatinine clearance	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
7.1 At up to 6 months	1		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
8 Inulin clearance	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
8.1 At up to 6 months	1		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
9 Glomeruli with mesangial widening	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
9.1 At up to 6 months	1		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
10 Glomeruli with segmental sclerosis	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
10.1 At up to 6 months	1		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
11 Obsolescent glomeruli	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
11.1 At up to 6 months	1		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
12 Echocardiographic data on left ventricular structure and function over 3 months and up to 6 months	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
12.1 Mean left ventricular wall thickness (mm)	1		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
12.2 Left ventricular internal diameter (mm) (diastolic)	1		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
12.3 Left ventricular internal diameter (mm) (systolic)	1		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
12.4 Left ventricular ejection fraction	1		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]

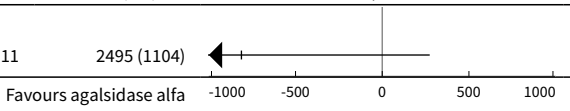
Analysis 1.1. Comparison 1 Agalsidase alfa vs placebo, Outcome 1 Plasma Gb3.

Study or subgroup	Agalsidase-alfa N	Agalsidase-alfa Mean(SD)	Placebo N	Placebo Mean(SD)	Mean Difference Random, 95% CI	Weight	Mean Difference Random, 95% CI
1.1.1 At up to 6 months							
Schiffmann 2001	14	5.6 (2)	11	10.2 (4.2)		45.79%	-4.61[-7.31,-1.91]
Hughes 2008	6	0.7 (0.5)	8	0.6 (0.3)		54.21%	0.07[-0.35,0.49]
Subtotal ***	**20**		**19**			**100%**	**-2.07[-6.64,2.5]**
Heterogeneity: Tau^2=9.98; Chi^2=11.31, df=1(P=0); I^2=91.16%							
Test for overall effect: Z=0.89(P=0.37)							



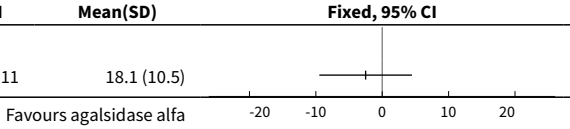
Analysis 1.2. Comparison 1 Agalsidase alfa vs placebo, Outcome 2 Urine sediment Gb3.

Study or subgroup	Agalsidase alfa N	Agalsidase alfa Mean(SD)	Placebo N	Placebo Mean(SD)	Mean Difference Fixed, 95% CI	Mean Difference Fixed, 95% CI
1.2.1 At up to 6 months						
Schiffmann 2001	14	1683 (1657)	11	2495 (1104)		-812[-1897.83,273.83]



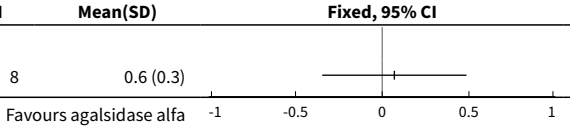
Analysis 1.3. Comparison 1 Agalsidase alfa vs placebo, Outcome 3 Kidney Gb3.

Study or subgroup	Agalsidase alfa N	Agalsidase alfa Mean(SD)	Placebo N	Placebo Mean(SD)	Mean Difference Fixed, 95% CI	Mean Difference Fixed, 95% CI
1.3.1 At up to 6 months						
Schiffmann 2001	14	15.6 (6)	11	18.1 (10.5)		-2.5[-9.47,4.47]



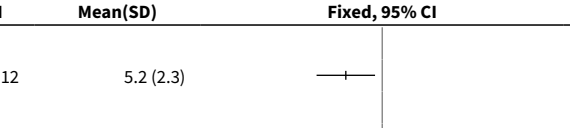
Analysis 1.4. Comparison 1 Agalsidase alfa vs placebo, Outcome 4 Myocardial globotriaosylceramide levels.

Study or subgroup	Agalsidase alfa N	Agalsidase alfa Mean(SD)	Placebo N	Placebo Mean(SD)	Mean Difference Fixed, 95% CI	Mean Difference Fixed, 95% CI
1.4.1 Over 3 months and up to 6 months						
Hughes 2008	6	0.7 (0.5)	8	0.6 (0.3)		0.07[-0.35,0.49]

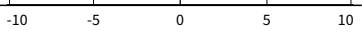


Analysis 1.5. Comparison 1 Agalsidase alfa vs placebo, Outcome 5 The Brief Pain Inventory Severity.

Study or subgroup	Agalsidase alfa N	Agalsidase alfa Mean(SD)	Placebo N	Placebo Mean(SD)	Mean Difference Fixed, 95% CI	Mean Difference Fixed, 95% CI
1.5.1 Over 1 month and up to 3 months						
Schiffmann 2001	14	3.1 (2)	12	5.2 (2.3)		-2.1[-3.79,-0.41]
1.5.2 Over 3 months and up to 5 months						



Study or subgroup	Agalsidase alfa N	Agalsidase alfa Mean(SD)	Placebo N	Placebo Mean(SD)	Mean Difference Fixed, 95% CI	Mean Difference Fixed, 95% CI
Schiffmann 2001	14	3.3 (2.5)	12	5.2 (2)		-1.9[-3.65,-0.15]
1.5.3 Over 5 months and up to 6 months						
Schiffmann 2001	14	2.7 (2)	12	4.7 (2.3)		-2[-3.66,-0.34]



Favours agalsidase alfa Favours placebo

Analysis 1.6. Comparison 1 Agalsidase alfa vs placebo, Outcome 6 The Brief Pain Inventory pain-related QoL.

Study or subgroup	Agalsidase alfa N	Agalsidase alfa Mean(SD)	Placebo N	Placebo Mean(SD)	Mean Difference Fixed, 95% CI	Mean Difference Fixed, 95% CI
1.6.1 Over 1 month and up to 3 months						
Schiffmann 2001	14	3.2 (2.3)	12	4.1 (2.5)		-0.9[-2.73,0.93]
1.6.2 Over 3 months and up to 5 months						
Schiffmann 2001	14	2.8 (2.5)	12	4.6 (2.6)		-1.8[-3.77,0.17]
1.6.3 Over 5 months and up to 6 months						
Schiffmann 2001	14	2.1 (2.1)	12	4.2 (2.6)		-2.1[-3.92,-0.28]

Favours agalsidase alfa Favours placebo

Analysis 1.7. Comparison 1 Agalsidase alfa vs placebo, Outcome 7 Creatinine clearance.

Study or subgroup	Agalsidase alfa N	Agalsidase alfa Mean(SD)	Placebo N	Placebo Mean(SD)	Mean Difference Fixed, 95% CI	Mean Difference Fixed, 95% CI
1.7.1 At up to 6 months						
Schiffmann 2001	13	94.8 (27.8)	11	84.5 (35.2)		10.3[-15.37,35.97]

Favours agalsidase alfa Favours placebo

Analysis 1.8. Comparison 1 Agalsidase alfa vs placebo, Outcome 8 Inulin clearance.

Study or subgroup	Agalsidase alfa N	Agalsidase alfa Mean(SD)	Placebo N	Placebo Mean(SD)	Mean Difference Fixed, 95% CI	Mean Difference Fixed, 95% CI
1.8.1 At up to 6 months						
Schiffmann 2001	13	71 (16.1)	11	71.5 (32)		-0.5[-21.36,20.36]

Favours agalsidase alfa Favours placebo

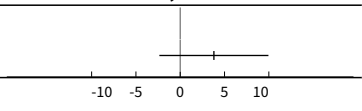
Analysis 1.9. Comparison 1 Agalsidase alfa vs placebo, Outcome 9 Glomeruli with mesangial widening.

Study or subgroup	Agalsidase alfa N	Agalsidase alfa Mean(SD)	Placebo N	Placebo Mean(SD)	Mean Difference Fixed, 95% CI	Mean Difference Fixed, 95% CI
1.9.1 At up to 6 months						
Schiffmann 2001	12	25.7 (20.8)	9	40.4 (28.5)		-14.7[-36.72,7.32]

Favours agalsidase alfa Favours placebo

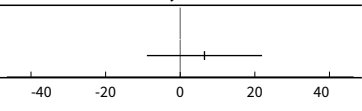
Analysis 1.10. Comparison 1 Agalsidase alfa vs placebo, Outcome 10 Glomeruli with segmental sclerosis.

Study or subgroup	Agalsidase alfa N	Agalsidase alfa Mean(SD)	Placebo N	Placebo Mean(SD)	Mean Difference Fixed, 95% CI	Mean Difference Fixed, 95% CI
1.10.1 At up to 6 months						
Schiffmann 2001	12	6.8 (8.7)	9	3 (5.7)		3.8[-2.35,9.95]



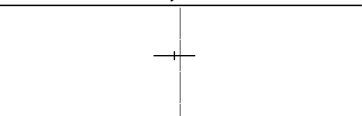
Analysis 1.11. Comparison 1 Agalsidase alfa vs placebo, Outcome 11 Obsolescent glomeruli.

Study or subgroup	Agalsidase alfa N	Agalsidase alfa Mean(SD)	Placebo N	Placebo Mean(SD)	Mean Difference Fixed, 95% CI	Mean Difference Fixed, 95% CI
1.11.1 At up to 6 months						
Schiffmann 2001	12	19.5 (20.8)	9	13 (15.3)		6.5[-8.93,21.93]



Analysis 1.12. Comparison 1 Agalsidase alfa vs placebo, Outcome 12 Echocardiographic data on left ventricular structure and function over 3 months and up to 6 months.

Study or subgroup	Agalsidase alfa N	Agalsidase alfa Mean(SD)	Placebo N	Placebo Mean(SD)	Mean Difference Fixed, 95% CI	Mean Difference Fixed, 95% CI
1.12.1 Mean left ventricular wall thickness (mm)						
Hughes 2008	6	12.6 (2.2)	8	13.4 (3.2)		-0.79[-3.62,2.04]
1.12.2 Left ventricular internal diameter (mm) (diastolic)						
Hughes 2008	6	48.4 (6.2)	8	52.1 (9.1)		-3.7[-11.73,4.33]
1.12.3 Left ventricular internal diameter (mm) (systolic)						
Hughes 2008	6	27.7 (5.9)	8	30.4 (7.9)		-2.7[-9.91,4.51]
1.12.4 Left ventricular ejection fraction						
Hughes 2008	6	81 (6.7)	8	79.1 (5.4)		1.88[-4.68,8.44]



Comparison 2. Agalsidase beta vs placebo

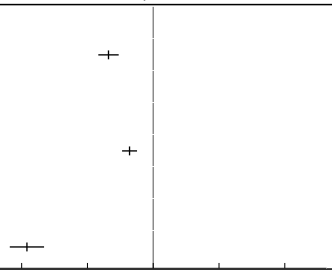
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Microvascular endothelial deposits of globotriaosylceramide	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
1.1 Kidney - over 3 months and up to 6 months	1		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1.2 Heart - over 3 months and up to 6 months	1		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
1.3 Composite - over 3 months and up to 6 months	1		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
2 Death (ITT population)	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
3 Renal events (ITT population)	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
4 Cardiopulmonary exercise test	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
4.1 Average heart rate reserve	1		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
4.2 Average maximum oxygen uptake measured at peak exercise (L/min)	1		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
4.3 Maximum oxygen uptake measured at peak exercise (ml/kg/min)	1		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
4.4 Oxygen pulse average at peak exercise	1		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
5 Cardiopulmonary exercise test	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
5.1 Decrease in diastolic blood pressure	1		Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
6 Cardiac events	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
7 Cerebrovascular events (ITT population)	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
8 Participants achieving zero scores in skin over 3 months and up to 6 months	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
8.1 Superficial endothelial cells	1		Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
8.2 Deep endothelial cells	1		Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
8.3 Smooth muscle cells	1		Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
8.4 Perineurium	1		Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
9 Participants achieving zero score or reduction in skin over 3 months and up to 6 months	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
9.1 Superficial endothelial cells	1		Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
9.2 Deep endothelial cells	1		Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
9.3 Smooth muscle cells	1		Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
9.4 Perineurium	1		Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
10 Chest pain	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
10.1 At 24 months	1		Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
11 Pain related to AFD	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
11.1 Over 3 and up to 6 months	1		Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
12 Fatigue	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
12.1 At 24 months	1		Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
13 Adverse event: rigors	2		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
13.1 Over 3 and up to 6 months	1		Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
13.2 At 24 months	1		Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
14 Adverse event: fever	2		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
14.1 Over 3 and up to 6 months	1		Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
14.2 At 24 months	1		Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
15 Adverse event: chills	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
15.1 Over 3 and up to 6 months	1		Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
16 Adverse event: hypertension	2		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
16.1 Over 3 and up to 6 months	1		Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
16.2 At 24 months	1		Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
17 Adverse event: vomiting	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
17.1 At 24 months	1		Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
18 Adverse event: headache	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
18.1 Over 3 and up to 6 months	1		Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]

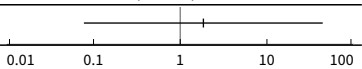
Analysis 2.1. Comparison 2 Agalsidase beta vs placebo, Outcome 1 Microvascular endothelial deposits of globotriaosylceramide.

Study or subgroup	Agalsidase beta N	Agalsidase beta Mean(SD)	Placebo N	Placebo Mean(SD)	Mean Difference Fixed, 95% CI	Mean Difference Fixed, 95% CI
2.1.1 Kidney - over 3 months and up to 6 months						
Eng 2001	29	0.4 (0.7)	29	2.1 (0.8)		-1.7[-2.09,-1.31]
2.1.2 Heart - over 3 months and up to 6 months						
Eng 2001	29	0.3 (0.5)	29	1.2 (0.6)		-0.9[-1.18,-0.62]
2.1.3 Composite - over 3 months and up to 6 months						
Eng 2001	29	0.7 (0.8)	29	5.5 (1.6)		-4.8[-5.45,-4.15]



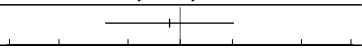
Analysis 2.2. Comparison 2 Agalsidase beta vs placebo, Outcome 2 Death (ITT population).

Study or subgroup	Agalsidase beta n/N	Placebo n/N	Risk Ratio M-H, Fixed, 95% CI	Risk Ratio M-H, Fixed, 95% CI
Banikazemi 2007	1/51	0/31		1.85[0.08,43.96]



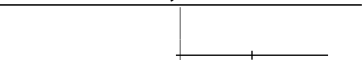
Analysis 2.3. Comparison 2 Agalsidase beta vs placebo, Outcome 3 Renal events (ITT population).

Study or subgroup	Agalsidase beta n/N	Placebo n/N	Risk Ratio M-H, Fixed, 95% CI	Risk Ratio M-H, Fixed, 95% CI
Banikazemi 2007	10/51	7/31		0.87[0.37,2.04]



Analysis 2.4. Comparison 2 Agalsidase beta vs placebo, Outcome 4 Cardiopulmonary exercise test.

Study or subgroup	Agalsidase beta N	Agalsidase beta Mean(SD)	Placebo N	Placebo Mean(SD)	Mean Difference Fixed, 95% CI	Mean Difference Fixed, 95% CI
2.4.1 Average heart rate reserve						
Bierer 2006	4	33.8 (13.1)	2	12.5 (13.4)		21.3[-1.28,43.88]
2.4.2 Average maximum oxygen uptake measured at peak exercise (L/min)						
Bierer 2006	4	1.7 (0.7)	2	1.5 (0.7)		0.22[-0.94,1.38]
2.4.3 Maximum oxygen uptake measured at peak exercise (ml/kg/min)						
Bierer 2006	4	22.4 (13.2)	2	19.8 (6.5)		2.6[-13.16,18.36]
2.4.4 Oxygen pulse average at peak exercise						
Bierer 2006	4	10.8 (3.4)	2	8.7 (3.4)		2.1[-3.67,7.87]

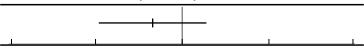


Analysis 2.5. Comparison 2 Agalsidase beta vs placebo, Outcome 5 Cardiopulmonary exercise test.

Study or subgroup	Agalsidase beta n/N	Placebo n/N	Risk Ratio M-H, Fixed, 95% CI	Risk Ratio M-H, Fixed, 95% CI
2.5.1 Decrease in diastolic blood pressure				
Bierer 2006	3/4	1/2		1.5[0.34,6.7]

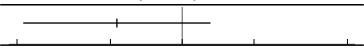
Analysis 2.6. Comparison 2 Agalsidase beta vs placebo, Outcome 6 Cardiac events.

Study or subgroup	Agalsidase beta n/N	Placebo n/N	Risk Ratio M-H, Fixed, 95% CI	Risk Ratio M-H, Fixed, 95% CI
Banikazemi 2007	3/51	4/31		0.46[0.11,1.9]



Analysis 2.7. Comparison 2 Agalsidase beta vs placebo, Outcome 7 Cerebrovascular events (ITT population).

Study or subgroup	Agalsidase beta n/N	Placebo n/N	Risk Ratio M-H, Fixed, 95% CI	Risk Ratio M-H, Fixed, 95% CI
Banikazemi 2007	0/51	2/31		0.12[0.01,2.48]



Analysis 2.8. Comparison 2 Agalsidase beta vs placebo, Outcome 8 Participants achieving zero scores in skin over 3 months and up to 6 months.

Study or subgroup	Agalsidase beta n/N	Placebo n/N	Risk Ratio M-H, Fixed, 95% CI	Risk Ratio M-H, Fixed, 95% CI
2.8.1 Superficial endothelial cells				
Eng 2001	29/29	1/29		19.67[4.13,93.63]
2.8.2 Deep endothelial cells				
Eng 2001	22/26	2/26		11[2.88,42.08]
2.8.3 Smooth muscle cells				
Eng 2001	1/3	0/1		1.5[0.1,22.62]
2.8.4 Perineurium				
Eng 2001	1/23	1/24		1.04[0.07,15.72]

Analysis 2.9. Comparison 2 Agalsidase beta vs placebo, Outcome 9 Participants achieving zero score or reduction in skin over 3 months and up to 6 months.

Study or subgroup	Agalsidase beta n/N	Placebo n/N	Risk Ratio M-H, Fixed, 95% CI	Risk Ratio M-H, Fixed, 95% CI
2.9.1 Superficial endothelial cells				
Eng 2001	29/29	10/29		2.81[1.72,4.59]
2.9.2 Deep endothelial cells				
Eng 2001	26/26	9/26		2.79[1.67,4.67]
2.9.3 Smooth muscle cells				
Eng 2001	1/3	0/1		1.5[0.1,22.62]
2.9.4 Perineurium				
Eng 2001	10/23	7/24		1.49[0.68,3.25]

Analysis 2.10. Comparison 2 Agalsidase beta vs placebo, Outcome 10 Chest pain.

Study or subgroup	Agalsidase beta n/N	Placebo n/N	Risk Ratio M-H, Fixed, 95% CI	Risk Ratio M-H, Fixed, 95% CI
2.10.1 At 24 months				
Banikazemi 2007	5/51	0/31		6.77[0.39,118.36]

Analysis 2.11. Comparison 2 Agalsidase beta vs placebo, Outcome 11 Pain related to AFD.

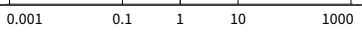
Study or subgroup	Agalsidase beta n/N	Placebo n/N	Risk Ratio M-H, Fixed, 95% CI	Risk Ratio M-H, Fixed, 95% CI
2.11.1 Over 3 and up to 6 months				
Eng 2001	3/29	1/29		3[0.33,27.18]

Analysis 2.12. Comparison 2 Agalsidase beta vs placebo, Outcome 12 Fatigue.

Study or subgroup	Agalsidase beta n/N	Placebo n/N	Risk Ratio M-H, Fixed, 95% CI	Risk Ratio M-H, Fixed, 95% CI
2.12.1 At 24 months				
Banikazemi 2007	5/51	0/31		6.77[0.39,118.36]

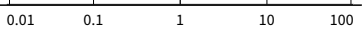
Analysis 2.13. Comparison 2 Agalsidase beta vs placebo, Outcome 13 Adverse event: rigors.

Study or subgroup	Agalsidase beta n/N	Placebo n/N	Risk Ratio M-H, Fixed, 95% CI	Risk Ratio M-H, Fixed, 95% CI
2.13.1 Over 3 and up to 6 months				
Eng 2001	14/29	0/29		29[1.81,464.38]
2.13.2 At 24 months				
Banikazemi 2007	18/51	1/31		10.94[1.54,77.95]



Analysis 2.14. Comparison 2 Agalsidase beta vs placebo, Outcome 14 Adverse event: fever.

Study or subgroup	Agalsidase beta n/N	Placebo n/N	Risk Ratio M-H, Fixed, 95% CI	Risk Ratio M-H, Fixed, 95% CI
2.14.1 Over 3 and up to 6 months				
Eng 2001	7/29	1/29		7[0.92,53.36]
2.14.2 At 24 months				
Banikazemi 2007	14/51	1/31		8.51[1.18,61.58]



Analysis 2.15. Comparison 2 Agalsidase beta vs placebo, Outcome 15 Adverse event: chills.

Study or subgroup	Agalsidase beta n/N	Placebo n/N	Risk Ratio M-H, Fixed, 95% CI	Risk Ratio M-H, Fixed, 95% CI
2.15.1 Over 3 and up to 6 months				
Eng 2001	4/29	0/29		9[0.51,159.94]

Analysis 2.16. Comparison 2 Agalsidase beta vs placebo, Outcome 16 Adverse event: hypertension.

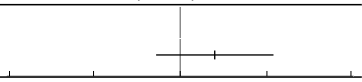
Study or subgroup	Agalsidase beta n/N	Placebo n/N	Risk Ratio M-H, Fixed, 95% CI	Risk Ratio M-H, Fixed, 95% CI
2.16.1 Over 3 and up to 6 months				
Eng 2001	3/29	0/29		7[0.38,129.74]
2.16.2 At 24 months				
Banikazemi 2007	7/51	2/31		2.13[0.47,9.6]

Analysis 2.17. Comparison 2 Agalsidase beta vs placebo, Outcome 17 Adverse event: vomiting.

Study or subgroup	Agalsidase beta n/N	Placebo n/N	Risk Ratio M-H, Fixed, 95% CI	Risk Ratio M-H, Fixed, 95% CI
2.17.1 At 24 months				
Banikazemi 2007	6/51	0/31		8[0.47,137.27]

Analysis 2.18. Comparison 2 Agalsidase beta vs placebo, Outcome 18 Adverse event: headache.

Study or subgroup	Agalsidase beta n/N	Placebo n/N	Risk Ratio M-H, Fixed, 95% CI	Risk Ratio M-H, Fixed, 95% CI
2.18.1 Over 3 and up to 6 months				
Eng 2001	5/29	2/29		2.5[0.53,11.86]

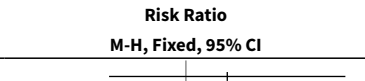


Comparison 3. Agalsidase alfa vs agalsidase beta

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Death	1		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
2 Cardiac events	1		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
3 Any adverse event	1		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
4 Any serious adverse events	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
4.1 New Subgroup	1		Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]

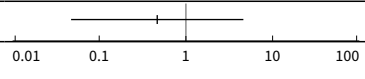
Analysis 3.1. Comparison 3 Agalsidase alfa vs agalsidase beta, Outcome 1 Death.

Study or subgroup	Agalsidase alfa n/N	Agalsidase beta n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
Vedder 2007	1/18	0/18		0%	3[0.13,69.09]



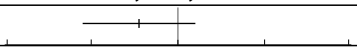
Analysis 3.2. Comparison 3 Agalsidase alfa vs agalsidase beta, Outcome 2 Cardiac events.

Study or subgroup	Agalsidase alfa n/N	Agalsidase beta n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
Vedder 2007	1/15	2/14		0%	0.47[0.05,4.6]



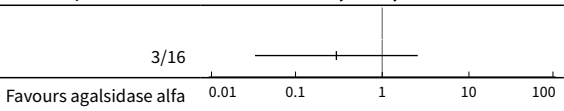
Analysis 3.3. Comparison 3 Agalsidase alfa vs agalsidase beta, Outcome 3 Any adverse event.

Study or subgroup	Agalsidase alfa n/N	Agalsidase beta n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
Vedder 2007	2/18	5/16		0%	0.36[0.08,1.59]



Analysis 3.4. Comparison 3 Agalsidase alfa vs agalsidase beta, Outcome 4 Any serious adverse events.

Study or subgroup	Agalsidase alfa n/N	Agalsidase beta n/N	Risk Ratio M-H, Fixed, 95% CI	Risk Ratio M-H, Fixed, 95% CI
3.4.1 New Subgroup				
Vedder 2007	1/18	3/16		0.3[0.03,2.57]

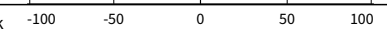


Comparison 4. 0.2 mg/kg/every 2 weeks vs 0.1 mg/kg/every week

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Pain	1		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
2 Self-assessed health state	1		Mean Difference (IV, Fixed, 95% CI)	Subtotals only

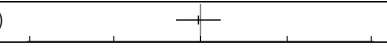
Analysis 4.1. Comparison 4 0.2 mg/kg/every 2 weeks vs 0.1 mg/kg/every week, Outcome 1 Pain.

Study or subgroup	0.2 mg/kg/every 2 weeks N	0.2 mg/kg/every 2 weeks Mean(SD)	0.1 mg/kg/every week N	0.1 mg/kg/every week Mean(SD)	Mean Difference Fixed, 95% CI	Weight	Mean Difference Fixed, 95% CI
Hughes 2013	18	1.7 (2.1)	18	1.6 (2)		0%	0.06[-1.26,1.38]



Analysis 4.2. Comparison 4 0.2 mg/kg/every 2 weeks vs 0.1 mg/kg/every week, Outcome 2 Self-assessed health state.

Study or subgroup	0.2 mg/kg/every 2 weeks N	0.2 mg/kg/every 2 weeks Mean(SD)	0.1 mg/kg/every week N	0.1 mg/kg/every week Mean(SD)	Mean Difference Fixed, 95% CI	Weight	Mean Difference Fixed, 95% CI
Hughes 2013	18	74.3 (20)	18	75.5 (19.5)		0%	-1.2[-14.1,11.7]



Comparison 5. 0.1 mg/kg/every week vs 0.2 mg/kg/every week

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Pain	1		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
2 Self-assessed health state	1		Mean Difference (IV, Fixed, 95% CI)	Subtotals only

Analysis 5.1. Comparison 5 0.1 mg/kg/every week vs 0.2 mg/kg/every week, Outcome 1 Pain.

Study or subgroup	0.1 mg/kg/every week		0.2 mg/kg/every week		Mean Difference	Weight	Mean Difference
	N	Mean(SD)	N	Mean(SD)	Fixed, 95% CI		Fixed, 95% CI
Hughes 2013	18	1.6 (2)	18	1.6 (2)		0%	0.06[-1.25,1.37]

Favours 0.2 mg/kg/week -100 -50 0 50 100 Favours 0.1 mg/kg/week

Analysis 5.2. Comparison 5 0.1 mg/kg/every week vs 0.2 mg/kg/every week, Outcome 2 Self-assessed health state.

Study or subgroup	0.1 mg/kg/every week		0.2 mg/kg/every week		Mean Difference	Weight	Mean Difference
	N	Mean(SD)	N	Mean(SD)	Fixed, 95% CI		Fixed, 95% CI
Hughes 2013	18	75.5 (19.5)	18	75.2 (20.3)		0%	0.3[-12.7,13.3]

Favours 0.2 mg/kg/week -100 -50 0 50 100 Favours 0.1 mg/kg/week

APPENDICES

Appendix 1. Glossary

Term	Explanation
Acroparaesthesia	Pain, tingling and numbness of the hands and forearms
Angiokeratoma	Skin condition characterized by intradermal hemangioma over which there is thickening of the epidermis
Angiokeratoma corporis diffusum	X-linked disorder caused by a deficiency of the lysosomal enzyme alpha-galactosidase A, also known as Anderson-Fabry disease
Cardiac	Relating to the the heart
Catabolism	The breaking down in living organisms of more complex substances into simpler ones
Cerebro-vascular disease	Group of brain dysfunctions related to disease, usually an obstruction, of the blood vessels supplying the brain

(Continued)

Deacylated	Describing a compound from which one or more acyl groups (an organic radical derived from an organic acid by the removal of the carboxylic hydroxyl group) has been removed
Dermatologic	Relating to the skin
Dyspnoea	Debilitating symptom or experience of unpleasant or uncomfortable respiratory (breathing) sensations
Echocardiography	Standard ultrasound techniques imaging two-dimensional slices of the heart to diagnose cardiovascular disease
Electrocardiography	Transthoracic interpretation of the electrical activity of the heart captured and externally recorded by skin electrodes
Endothelial	Thin layer of cells that line the interior surface of blood vessels
Gastrointestinal	Relating to the digestive system
Globotriaosylceramide	Type of glycolipid compound which accumulates in the blood vessel walls of people with Fabry disease as a result of a deficiency in alpha-galactosidase A, a lysosomal enzyme
Glomerular filtration rate	Volume of fluid filtered from the renal (kidney) glomerular capillaries into the Bowman´s capsule (a cup-like sac at the beginning of the tubular component of a nephron in the mammalian kidney) per unit time
Glomeruli	Capillary tuft surrounded by Bowman's capsule in nephrons of the vertebrate kidney
Glycolipid	Any of a group of lipids containing a carbohydrate group, commonly glucose or galactose
GlycosphingolipidIt	Subtype of glycolipids containing the amino alcohol sphingosine; a ceramide (a sphingolipid) linked to one or more sugars via the terminal hydroxyl group
Hemangioma	A congenital benign skin lesion consisting of dense, usually elevated masses of dilated blood vessels
IgE antibodies	Type of immunoglobulin made by the body which are implicated in allergic reactions
IgG antibodies	Type of immunoglobulin involved in fighting foreign bodies, bacterial and viral infections
Left ventricular ejection fraction	Fraction of blood pumped out of the left ventricle with each heart beat
Lyonization	Phenomenon wherein one of the two copies of the X chromosome present in female mammals is inactivated
Lysosomal hydrolase alpha-galactosidase	Enzyme involved in glycolipid catabolism, which requires an acidic environment as maintained in the lysosome
Lysosomal inclusions	Storage bodies associated with lysosomal dysfunction, usually a deficiency of an enzyme involved in catabolism
Lysosome	Any of numerous small particles, containing digestive enzymes, that are present in the cytoplasm of most cells
Mammalian cell expression system	Elements involved in the translation of genetic information to form a particular protein

(Continued)

Mesangial widening	Thickening of the mesangium, a part of the renal glomerulus between capillaries
Microvascular disease	Angiopathy or condition affecting small blood vessels in the body
Myocardial infarction	Commonly known as a heart attack, resulting from an interruption of blood supply to part of the heart
Nephron	Any of the minute urine-secreting tubules that form the functional unit of the kidneys
Neurologic disease	Disorder of the brain, spinal cord and nerves
Neuropathic	Referring to disorders of the peripheral nervous system
Parametric data	Parametric statistical tests assume that the data are 'normally distributed', that is, when graphed, the data follow a 'bell shaped curve'
Perineurium cells	Cells from the perineurium, the middle layer of the protective perineural sheath surrounding peripheral nerves
Proteinuria	Presence of an excess of serum proteins in the urine
Renal	Relating to the kidneys
Segmental sclerosis	Scarring or degeneration, often used in relation to disease of a kidney section
Sero-converted	Development of antibodies in the blood as a result of the introduction of a foreign body, infection or immunization
Serum creatinine	By-product of metabolism that is measured in serum as a indicator of kidney function
Substrate	Molecule that is acted upon by an enzyme
Thrombo-embolic	Blocking of a blood vessel by a blood clot dislodged from its site of origin
Transduced	Conversion of one type of energy or signal into another; in genetics the introduction of DNA into a different cell type, to induce the formation of the corresponding gene product
Transthoracic echocardiogram	A test that uses high frequency sound waves, called ultrasound, to examine and take pictures of your heart
Urinary albumin	Presence of albumin, a protein, in the urine
X-linked	Relating to genes or characteristics or conditions carried on the X chromosome

Appendix 2. Search strategy - Clinical Trials (*The Cochrane Library*, Issue 9, 2015)

Search Strategy
((Fabry Disease) OR (Disease, Fabry) OR (Angiokeratoma Corporis Diffusum) OR (Anderson-Fabry Disease) OR (Anderson Fabry Disease) OR (Disease, Anderson-Fabry) OR (Fabry's Disease) OR (Disease, Fabry's) OR (Fabrys Disease)) AND ((agalsidase beta) OR (Fabrazyme) OR (Genzyme brand of agalsidase beta))

Appendix 3. Search strategy - EMBASE (1980 - 24 September 2015)

Search Strategy
1. Randomized controlled trial/
2. Controlled study/
3. Randomization/
4. Double blind procedure/
5. Single blind procedure/
6. Clinical trial/
7. (clinical adj5 trial$).ti,ab,hw.
8. ((doubl$ or singl$ or tripl$ or trebl$) adj5 (blind$ or mask$)).ti,ab,hw.
9. Placebo/
10. Placebo$.ti,ab,hw.
11. Random$.ti,ab,hw.
12. Methodology.sh.
13. latin square.ti,ab,hw.
14. crossover.ti,ab,hw.
15. cross-over.ti,ab,hw.
16. Crossover Procedure/
17. Drug comparison/
18. Comparative study/
19. (comparative adj5 trial$).ti,ab,hw.
20. (control$ or prospectiv$ or volunteer$).ti,ab,hw.
21. exp "Evaluation and Follow Up"/
22. Prospective study/
23. or/1-22
24. animal/ not (human/ and animal/)
25. 23 not 24
26. ((Fabry Disease) OR (Disease, Fabry) OR (Angiokeratoma Corporis Diffusum) OR (Anderson-Fabry Disease) OR (Anderson Fabry Disease) OR (Disease, Anderson-Fabry) OR (Fabry's Disease) OR (Disease, Fabry's) OR (Fabrys Disease)) AND ((agalsidase beta) OR (Fabrazyme) OR (Genzyme brand of AGAL) OR (Agalsidase alfa) OR (Replagal) OR (Shire HGT brand of AGAL))
27. 25 and 26

Appendix 4. Search strategy - PubMed (1966 - 24 September 2015)

Search Strategy
(((Fabry Disease) OR (Disease, Fabry) OR (Angiokeratoma Corporis Diffusum) OR (Anderson-Fabry Disease) OR (Anderson Fabry Disease) OR (Disease, Anderson-Fabry) OR (Fabry's Disease) OR (Disease, Fabry's) OR (Fabrys Disease)) AND ((agalsidase beta) OR (Fabrazyme) OR (Genzyme brand of AGAL) OR (Agalsidase alfa) OR (Replagal) OR (Shire HGT brand of AGAL))) AND (randomized controlled trial [Publication Type] OR controlled clinical trial [Publication Type] OR randomized controlled trials [MeSH Terms] OR random allocation [MeSH Terms] OR double blind method [MeSH Terms] OR single blind method [MeSH Terms] OR clinical trial [Publication Type] OR clinical trials [MeSH Terms] OR (clinical* [Text Word] AND trial* [Text Word]) OR single* [Text Word] OR double* [Text Word] OR treble* [Text Word] OR triple* [Text Word] OR placebos [MeSH Terms] OR placebo* [Text Word] OR random* [Text Word] OR research design [MeSH Terms] OR comparative study [MeSH Terms] OR evaluation studies [MeSH Terms] OR follow-up studies [MeSH Terms] OR prospective studies [MeSH Terms] OR control* [Text Word] OR prospectiv* [Text Word] OR volunteer* [Text Word])

Appendix 5. Search strategy - LILACS (1982 - 24 September 2015)

Search Strategy
(((Fabry Disease) OR (Disease, Fabry) OR (Angiokeratoma Corporis Diffusum) OR (Anderson-Fabry Disease) OR (Anderson Fabry Disease) OR (Disease, Anderson-Fabry) OR (Fabry's Disease) OR (Disease, Fabry's) OR (Fabrys Disease)) AND ((agalsidase beta) OR (Fabrazyme) OR (Genzyme brand of AGAL) OR (Agalsidase alfa) OR (Replagal) OR (Shire HGT brand of AGAL))) AND ((Pt randomized controlled trial) OR (Pt controlled clinical trial) OR (Mh randomized controlled trials) OR (Mh random allocation) OR (Mh double blind method) OR (Mh single blind method) AND NOT (Ct animal) AND NOT (Ct human and Ct animal) OR (Pt clinical trial) OR (Ex E05.318.760.535$) OR (Tw clin$) AND (Tw trial$) OR (Tw ensa$) OR (Tw estud$) OR (Tw experim$) OR (Tw investiga$) OR (Tw singl$) OR (Tw simple$) OR (Tw doubl$) OR (Tw doble$) OR (Tw duplo$) OR (Tw trebl$) OR (Tw trip$) AND (Tw blind$) OR (Tw cego$) OR (Tw ciego$) OR (Tw mask$) OR (Tw mascar$) OR (Mh placebos) OR (Tw placebo$) OR (Tw random$) OR (Tw randon$) OR (Tw casual$) OR (Tw acaso$) OR (Tw azar) OR (Tw aleator$) OR (Mh research design) AND NOT (Ct animal) AND NOT (Ct human and Ct animal) OR (Ct comparative study) OR (Ex E05.337$) OR (Mh follow-up studies) OR (Mh prospective studies) OR (Tw control$) OR (Tw prospectiv$) OR (Tw volunt$) OR (Tw volunteer$) AND NOT ((Ct animal) AND NOT (Ct human and Ct animal)))

WHAT'S NEW

Date	Event	Description
29 June 2017	Amended	Contact details updated.

HISTORY

Protocol first published: Issue 3, 2007
Review first published: Issue 5, 2010

Date	Event	Description
14 July 2016	New citation required but conclusions have not changed	The review update includes three new trials (Clarke 2007; Hughes 2013; Sirrs 2014). One trial compares agalsidase alfa to agalsidase beta (Sirrs 2014), and two compared multiple dosage regimens of agalsidase alfa (Clarke 2007; Hughes 2013). The inclusion of these trials did not significantly alter the conclusions of the review.

Date	Event	Description
14 July 2016	New search has been performed	A total of 17 potentially relevant references were identified by the search of the Group's Inborn Errors of Metabolism Register. We selected all references for careful consideration and obtained them in full text, when available. Following assessment of the full articles, we included three new clinical trials (Clarke 2007; Hughes 2013; Sirrs 2014) and excluded 12 further studies (Tsuboi 2014; Benjamin 2014; Fellgiebel 2014; Hughes 2014; Kim 2014; Schiffmann 2014; Weidemann 2014; Germain 2013; Tøndel 2013; Schiffmann 2013; Rombach 2012; Sirrs 2011). On further study has been added to studies awaiting classification (Wijburg 2015).
12 December 2012	New citation required but conclusions have not changed	Despite the addition of one new included trial, the conclusions remain the same as those in the original review (El Dib 2010).
12 December 2012	New search has been performed	One new trial has been included in the review (Vedder 2007). Two trials have been added to the excluded studies (Fernhoff 2011; West 2011). Data and information have been included for a 'Agalsidase alfa versus agalsidase beta' comparison group (Vedder 2007).
15 February 2012	Amended	Contact details updated.
15 February 2011	Feedback has been incorporated	Feedback, along with a response has been added to this review. In the Included studies section, the study IDs previously listed as Thurberg 2004 and Moore 2002 have been changed to Eng 2001 and Schiffmann 2001, to more accurately reflect the primary study reports. Furthermore, all outcomes reported by Hughes are now listed in full in the tables (Characteristics of included studies) (Hughes 2008). The Declarations of interest section has been updated.
20 September 2008	New citation required and conclusions have changed	Substantive amendment

CONTRIBUTIONS OF AUTHORS

Regina El Dib (RED) was responsible for the conception of this review and also for the design and overall co-ordination of the protocol. RED is the guarantor of the review.

Huda Goma (HG) and Raíssa Pierri Carvalho (RPC) were responsible for developing the search strategy, undertaking searches, screening search results, organising retrieval of papers. RED, HG and Paulo do Nascimento Junior (PNJ) were responsible for screening retrieved papers against the inclusion criteria, appraising quality of papers and extracting data. Samira Esteves Camargo (SEC) and Pasqual Barretti (PB) wrote to authors of papers for additional information and located potentially relevant unpublished or ongoing trials. SEC, PB and Fellype C Barreto (FCB) provided additional data about papers and obtained and screened data on unpublished trials. RED, HG, RPC and PB were responsible for data management for the review and entering data into RevMan. RED, HG, SEC, PB, PNJ and FCB analysed and interpreted the data and wrote up the results.

DECLARATIONS OF INTEREST

R El Dib, H Goma, RP Carvalho, SE Camargo, R Bazan, and FC Barreto have no conflicts of interest to declare.

P Barretti is a full professor of Sao Paulo State University at Botucatu School of Medicine and active member of the Regional Latin American Advisory Board of Baxter Healthcare Company.

SOURCES OF SUPPORT

Internal sources

- No sources of support supplied

External sources

- Provided by CAPES, Brazil.

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

The Assessment of risk of bias in included studies section was updated from the protocol given the new guidelines published in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011).

We decided for our secondary outcomes 'Pain' and 'QoL' we would also consider other validated questionnaires.

We decided that the secondary outcome 'Costs reported narratively' was not an appropriate outcome to be measured in this review of randomised controlled trials.

While analysing available data we agreed to also considered other time points as well as those originally stated where multiple data sets from an individual trial were available for a single *a priori* planned time point.

We decided for assessment of blinding that if a trial measured an objective outcome then lack of blinding was rated as low risk of bias.

INDEX TERMS

Medical Subject Headings (MeSH)

Enzyme Replacement Therapy [*methods]; Fabry Disease [*drug therapy] [enzymology]; Isoenzymes [*administration & dosage]; Pain Measurement; Randomized Controlled Trials as Topic; Recombinant Proteins; Time Factors; Trihexosylceramides [analysis] [blood]; alpha-Galactosidase [*administration & dosage]

MeSH check words

Female; Humans; Male